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In re reissue patent application of:	Art Unit: 1614
Zappala	Examiner: Jagoe, Donna A
Application No: 10/734,070	Current status of application:
(For reissue of Patent No.: 6,329,398)	Docketed New Case – Ready for
Filing of Application: 12/11/2003	Examination
For: Preemptive analgesic agent and	**ATTENTION: Bruce Kisliuk**
methods of use	

Protest Under 37 CFR 1.291(a)

APPROVED
for scanning
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SPRE

Assistant Commissioner for Patents
Washington, DC 20231

To whom it may concern:
This protest is being filed on a reissue application within the 2-month period following the announcement of the reissue application in the *Official Gazette* on June 29, 2004.

Pursuant to 37 CFR 1.291(b):

1) A listing of patent, publications, and other information relied upon can be found in the enclosed PTO-1449 form.

2) A concise explanation of the relevance of each listed item is included herewith.

3) A copy of each listed patent, publication, or other item of information in written form, or pertinent portions thereof is enclosed.

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Summary of documents

Non-patent literature

Vincent J. Collins, "Principles of anesthesiology: general and regional anesthesia," (Lea & Febiger, 3d ed. 1993), pp. 1238-1261.

Collins describes the anesthetic properties of lidocaine and bupivacaine. In particular, the dosages disclosed for bupivacaine are broken down by type of anesthetic procedure and by anatomy.

Michael J. Cousins, et al., "Neural blockade in clinical anesthesia and management of pain," (Lippincott-Raven, 3d ed. 1998), pp. 102-105, 122-23.

Cousins describes the conclusions of several research studies regarding the effects of mixing local anesthetics. In particular, Cousins describes the relationship between the pH of the mixture and the duration of the anesthetic effect.

*Clifford Y. Ko, et al., "Preemptive analgesia in patients undergoing appendectomy," Arch Surg (1997) 132:874-78.

Ko discloses the uses of a lidocaine-bupivacaine mixture for preemptive analgesia. Also disclosed are suggestions for modifying and improving the studied mixture.

David E. Longnecker, et al., "Introduction to anesthesia," (W.B. Saunders Company, 9th ed. 1997), pp. 209-211.

Longnecker discloses how to choose a local anesthetic mixture.

Ronald D. Miller, et al., 1 "Anesthesia," (Churchill Livingsone, 4th ed. 1994), pp. 504-508.

Miller generally describes the properties of local anesthetics. In particular, Miller discloses the possible and usual concentrations of lidocaine and bupivacaine in several types of anesthesia.

Naropin package insert, Astra USA, Inc. (Jan. 1999)

The Naropin insert is an example of how injectable anesthetics are used and sold. Specifically, it describes the drug as a sterile, isotonic solution which may have its pH adjusted by adding sodium hydroxide or hydrochloric acid.

L.T. Seow, et al., "Lidocaine and bupivacaine mixtures for epidural blockade," Anesthesiology (1982) 56:177-183.

Seow discloses how to make and use different ratios of a bupivacaine-lidocaine mixture.

* References already cited in the reissue application are not enclosed herewith.

Arguments

35 U.S.C. 112 Arguments

Claims 6, 10, and 23 should be rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicant claims the use of the analgesic agent in the performance of several anesthetic procedures, but does not disclose how the agent can be adapted for each of the claimed applications. The specification does not go beyond a bare assertion, "The agent is preferably an injectable therapy adapted for one or more applications" (specification, col. 1, lines 62-65).

Claims 8, 11, 15, 16, 22, and 31 should be rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. Applicant claims an anesthetic combination having a ratio between its two constitutive drugs such that the combination will provide at least six hours of analgesic effect. However, applicant does not disclose either what that ratio is or how to determine that ratio.

Solely for the sake of discussing further grounds for rejecting the above claims, the remainder of the arguments will presume that all claims are properly enabled.

35 U.S.C. 102 Arguments

Claim 1 should be rejected under 35 U.S.C. 102(b) as being anticipated by Miller. There are three elements recited in this claim: 1) the pharmacological agent is a solution comprising lidocaine HCl and bupivacaine HCl; 2) the lidocaine in the solution has a concentration of 1% and the bupivacaine in the solution has a concentration of 0.25%; 3) the ratio of lidocaine to bupivacaine in the solution is less than or equal to 10:1. All three of these elements are disclosed by Miller.

First, Miller describes both the general principle of combining anesthetics in solution, as well as a combination comprising lidocaine and bupivacaine. Miller states that the basis for mixing local anesthetics is to enable the artisan to "compensate for the short duration of action of certain rapidly acting agents such as chloroprocaine and lidocaine and the long latency of other agents such as tetracaine and bupivacaine" (Miller, 503, col. 2).

Second, it was already known in the art, as evidenced by Miller, that lidocaine and bupivacaine should be used in the claimed concentrations of 1.0% and 0.25%, respectively. For a minor nerve block, the disclosure of Miller

describes the claimed concentrations as "the usual concentrations" (Miller, 505, Table 15-5).

Third, the claimed range of lidocaine-bupivacaine ratios, equal to or less than 10:1, is anticipated by Miller. The disclosure of Miller is not limited to lidocaine-bupivacaine ratios greater than 10:1. Indeed, the "usual volume" of lidocaine and bupivacaine disclosed by Miller would allow for lidocaine-bupivacaine ratios of from 4:1 to 1:4 (Miller, 505). Referring to Table 15-5 in Miller, lidocaine and bupivacaine both have usual volumes of between 5 mL, and 20 mL (Miller, 505). Combinations involving the upper and lower limits of the range of usual volumes correspond to lidocaine-bupivacaine ratios of between 4:1 (20 mL lidocaine, 5 mL bupivacaine) and 1:4 (5 mL lidocaine, 20 mL bupivacaine).

Therefore, Claim 1 should be rejected as anticipated by Miller. In reference to Claims 2-4, ratios of less than 5:1, 2:1 and 1:1 are all anticipated by the 1:4 ratio disclosed in Miller. In reference to Claim 6, a minor nerve block is a type of peripheral nerve blockade (Miller, 505).

35 U.S.C. 103 Arguments

In addition to being anticipated under 35 U.S.C. 102(b), Claim 1 should be rejected under 35 U.S.C. 103(a) as unpatentable over Seow, in view of Miller. Seow discloses a composition which can be used to create an epidural blockade,

the composition containing 2% lidocaine and 0.5% bupivacaine in ratios of 3:1, 1:1, and 1:3 (Seow, 177). Seow does not teach the combination of 1% lidocaine and 0.5% bupivacaine. However, Miller discloses that to create an epidural blockade, the "usual concentration" range for lidocaine is 1-2% and the "usual concentration" range for bupivacaine is 0.25-0.75% (Miller, 506, Table 15-7). Therefore, a person having ordinary skill in the art would have been motivated to create a rapid-onset epidural blockade by using the lidocaine-bupivacaine combination of Seow, wherein the concentrations of lidocaine and bupivacaine are selected from the range of usual concentrations disclosed in Miller. In reference to Claims 2-4, Seow discloses a lidocaine-bupivacaine ratio of 1:3, which is equal to or less than each of the ratios claimed (Seow, 178, Table 1). In reference to Claim 6, Seow and Miller disclose the application of the solution to epidural blockades, as discussed above. In reference to Claim 7, Seow and Miller both disclose solutions for epidural blockades having epinephrine in the ratio of 1:200,000 (Seow, 178, Table 1; Miller, 506, Table 15-7).

In reference to Claim 8, Miller teaches that the administration of a composition containing 1:200,000 epinephrine and between 0.25% and 0.5% bupivacaine will create a major nerve block having a duration of between 360 and 720 minutes (Miller, 505, Table 15-6). Accordingly, administration of epinephrine with 0.25% bupivacaine will result in a major nerve block lasting for at least 6 hours. Miller does not teach the duration of a major nerve block that would result from administration of a composition having 1% lidocaine and 0.25%

bupivacaine. However, a person having ordinary skill in the art could have readily determined which lidocaine-bupivacaine ratios would produce a nerve block lasting for at least 6 hours. Indeed, it was a common practice in the art to choose mixtures of anesthetics based in part on the planned duration of anesthesia (Longnecker, 209, "Choosing a Local Anesthetic Mixture").

Claim 9 should be rejected under 35 U.S.C. 103(a) as unpatentable over Ko, in view of Miller. Ko teaches a method for reducing perioperative pain by injecting a preemptive analgesic solution before incision, wherein the preemptive analgesic used is a 1:1 mixture of 1% lidocaine and 0.5% bupivacaine (Ko, 875, "Patients and Methods"). The preincisional injection technique of Ko is infiltration into the dermis and subcutaneous tissues (Ko, 875, "Patients and Methods", col. 2, line 1). Ko contemplates but does not clearly teach a solution having 1% lidocaine, but only 0.25% bupivacaine (Ko, 877, col. 2, second full paragraph). However, Miller teaches that the usual concentration of bupivacaine for infiltration anesthesia is between 0.25% and 0.5%. (Miller, 505, Table 15-4). A person having ordinary skill in the art would have been motivated to apply the standard 0.25% concentration set out in Miller to the preemptive infiltration analgesic method of Ko, in order to create a more effective analgesic. Ko states, "Whether preemptive analgesia using a combination of analgesics . . . would be more successful in this patient population remains unknown at this time. Further studies are warranted in this regard" (Ko, 876). In reference to Claim 10, Ko discusses the use of an injectable peripheral nerve block (Ko, 878, col. 1, last

paragraph). Further, Collins teaches that use of 0.25% bupivacaine is preferred under specific circumstances for the techniques of infiltration, nerve block, caudal, and epidural block (Collins, 1260). In reference to Claim 11, Miller and Longnecker disclose an agent which may provide at least six hours of analgesic effect, as described in the analysis above for Claim 8. In reference to Claim 12, Miller generally describes the use of vasoconstrictors (Miller, 502) and specifically discloses the use of a vasoconstrictor, epinephrine, as an additive for peripheral nerve blockade (Miller, 505, Table 15-5 and Table 15-6). In reference to Claims 12 and 13, Ko suggests the use of both a buffered solution and a vasoconstrictor, epinephrine (Ko, 878, col. 1).

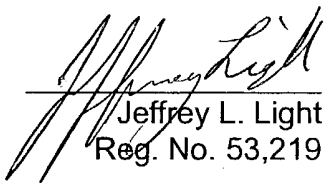
Claims 5 and 14 should be rejected under 35 U.S.C. 103(a) as unpatentable over Miller and Seow, in further view of Naropin Package Insert and Cousins. Miller and Seow teach a composition having 1% lidocaine and 0.25% bupivacaine in a ratio less that or equal to 10:1, as discussed in the analysis of Claim 1 above. It would have been obvious to a person having ordinary skill in the art that sodium hydroxide or hydrochloric acid could be added as a buffer, and used to alter the pH of an injectable anesthetic solution (Naropin Package Insert, "Description") for the purpose of increasing the duration of anesthetic effect (Cousins, 105, col.2). In reference to Claims 15 and 16, Miller and Longnecker teach the selection of an anesthetic mixture having a duration of at least 6 hours, as described in the analysis for Claim 8 above. In further reference to Claims 17-24, Longnecker teaches the use and advantages of

premixing the anesthetic with a buffer (Longnecker, 211). In reference to Claim 25, it would have been obvious to a person having ordinary skill in the art to adjust the pH of the solution to be about 7.4, because it is an inherent property of both blood and spinal fluid that they have a normal pH of 7.4. The method of accomplishing the pH change would also have been known to a person having ordinary skill in the art, as discussed in the analysis of Claim 14 above. In reference to claims 26-33, it would have been obvious to a person having ordinary skill in the art to make each of the compositions claimed, as discussed in the analysis of the preceding claims.

Conclusion

Protestor respectfully requests that claims 1-33 be rejected.

Respectfully submitted,



Jeffrey L. Light
Reg. No. 53,219

Date: 22 Mar, 2004
2101 16th St., NW, #102
Washington, DC 20009
(202)-277-6213

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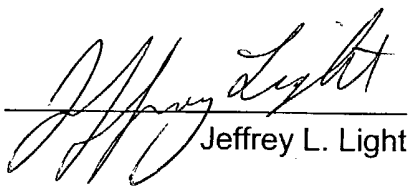

Jeffrey L. Light

Reg. No. 53,219
2101 16th St., NW #102
Washington, DC 20009
(202)277-6213

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Sheet 1 of 1

Complete if Known	
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First Named Inventor	ZAPPALA
Art Unit	1614
Examiner Name	JAGOE, DONNA A
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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		VINCENT J. COLLINS, "Principles of anesthesiology: general and regional anesthesia," (Lea & Febiger, 3d ed. 1993), pp. 1238-1261.	
		MICHAEL J. COUSINS, et al., "Neural blockade in clinical anesthesia and management of pain," (Lippincott-Raven, 3d ed. 1998), pp. 102-105, 122-23.	
		DAVID E. LONGNECKER, et al., "Introduction to anesthesia," (W.B. Saunders Company, 9th ed. 1997), pp. 209-211.	
		RONALD D. MILLER, et al., 1 "Anesthesia," (Churchill Livingsone, 4th ed. 1994), pp. 504-508.	
		NAROPIN package insert, Astra USA, Inc. (Jan. 1999)	
		L.T. SEOW, et al., "Lidocaine and bupivicaine mixtures for epidural blockade," Anesthesiology (1982) 56:177-183.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

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EDITOR

ANESTHESIA

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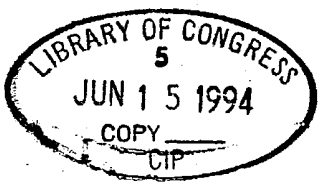

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nodes of Ranvier in sequence are depolarized to threshold with little intervening delay. Single impulses do not jump from node to node as separate, discrete events, but instead the active depolarization occurs simultaneously along several centimeters of the largest axons[11] (see Fig. 15-10). Indeed, the local circuit current is so robust that it can skip past two completely nonexcitable nodes and successfully stimulate a third.[12] If nodal excitability is partially reduced, by inhibition of some of the Na^+ channels for example, the amplitude of impulses in successive nodes falls decrementally, a process that can continue for many centimeters.[13] This situation probably occurs during certain phases of local anesthesia, as discussed below. When the extent of inhibition of Na^+ channels is sufficient, however, the impulse is extinguished.

MECHANISM OF ACTION OF LOCAL ANESTHETICS (PHARMACODYNAMICS)

Active Form

Local anesthetic bases are poorly to sparingly soluble in water but are soluble in relatively hydrophobic organic solvents. Therefore, as a matter of convenience most of these drugs are marketed as the hydrochloride salts, which are soluble in water but insoluble in organic solvents. The pK_a of the drug and the tissue pH determine the amount of drug that exists in solution as free base or as positively charged cation when injected into living tissue. Furthermore, the uptake of the drug by the tissue, due largely to lipophilic adsorption, will also alter its activity, both by shifting the effective pK_a downward, and thereby favoring the neutral base form, and by limiting the diffusion of the anesthetic away from the site of injection. Thus moderately hydrophobic local anesthetics will act more rapidly than either slightly hydrophobic or highly hydrophobic ones, delivered at the same concentration. Since the highly hydrophobic local anesthetics also have higher intrinsic potency[3] (see Table 15-2), they are delivered in lower amounts and their diffusion profile is correspondingly reduced, which compromises their rate of onset even further.

A lengthy debate has taken place over the issue of which form of the local anesthetic is actually responsible for prevention of impulse propagation. Early observations showed that alkaline solutions of local anesthetics more effectively blocked nerve conduction.[14] In the desheathed nerve and in the isolated single axon, the rate of inhibition by tertiary amine anesthetics also was greater at alkaline than at neutral external pH.[15,16] From these observations it was concluded that either the neutral base in the external solution is the active species or else membrane penetration and transport, highly favored by base over cation species, are essential for the channel blocking action. The second possibility is, in fact, the explanation for the acceleration of rate in alkaline media.[16,17] Direct control of axoplasmic pH[18] or internal perfusion with permanently charged quaternary amine homologues shows the dominant potency of the cationic species acting from the cytoplasmic surface.[19,20] The uncharged base also has pharmacologic activity, however, and not only molecules with tertiary amine moieties but also those having hydroxyl (alcohols) or alkyl groups (e.g., benzocaine) can inhibit Na^+ channels and block impulses.[16,17,21,22]

To obtain a clear picture of the mechanism, the inhibitory kinetics are necessary, but it is almost impossible to measure the rate of binding of local anesthetics to the receptor after their addition to a bathing solution. Drug diffusion through the unstirred layer of solution next to the membrane and the membrane itself present steps that limit the rate of receptor binding.[16,23] However, once the drug has equilibrated with membranes and solutions, it is possible to perturb the channels by depolarizing the membrane and to follow the "phasic" inhibition by local anesthetics in order to clarify the details of the binding reaction, as described below.

The Electrophysiologic Effect of Local Anesthetics

The resting membrane potential of nerve is little affected by local anesthetics.[24] As the concentration of local anesthetic applied to the nerve is increased, a decrease in the rate and degree of impulse depolarization is produced. However, neither the reduction of amplitude nor the rate of depolarization of an action potential is proportional to the fraction of Na^+ channels inhibited by local anesthetics. Therefore, it is not possible to derive direct data on the binding of local anesthetics from measurement of nerve impulses.

By using a voltage-clamp procedure, however, Na^+ currents and their inhibition by local anesthetics can be directly assayed (Fig. 15-8). When the membrane is rapidly depolarized to a constant value, the time course of currents is observed. Rapidly rising (activated) and subsequently declining (inactivated) Na^+ currents are reduced for one depolarization by subclinical doses of local anesthetic (e.g., 0.2 mM lidocaine) and completely inhibited by clinical doses (e.g., 1 percent lidocaine, which equals about 40 mM). If the test depolarization is repeatedly applied at frequencies above 5 Hz (5 pulses per second), the partially depressed Na^+ current is further reduced, incrementally for each pulse, until a new steady-state level of inhibition is reached.[20,25] This frequency-dependent inhibition, also called *phasic inhibition*, is reversed when stimulation is slowed or stopped, and currents return to the level of *tonic inhibition* observed in the resting nerve. The potency for local anesthetics to produce both tonic and phasic inhibition are dependent on their structure, hydrophobicity, and pK_a.[25,26] There thus appears to be a single binding site for local anesthetics on the Na^+ channel, with a tonic affinity at rest and increased phasic affinity occurring as a result of depolarization. The phasic blocking mode can thus be used to reveal the true kinetics of local anesthetic binding to the functional receptor, the Na^+ channel itself.

Na^+ currents are reduced by local anesthetics primarily because the drug-bound channels fail to open. Investigations with neutral and cationic compounds show that the channel activation process is disrupted by local anesthetics.[27,28] A sodium channel inhibited by a local anesthetic is functionally

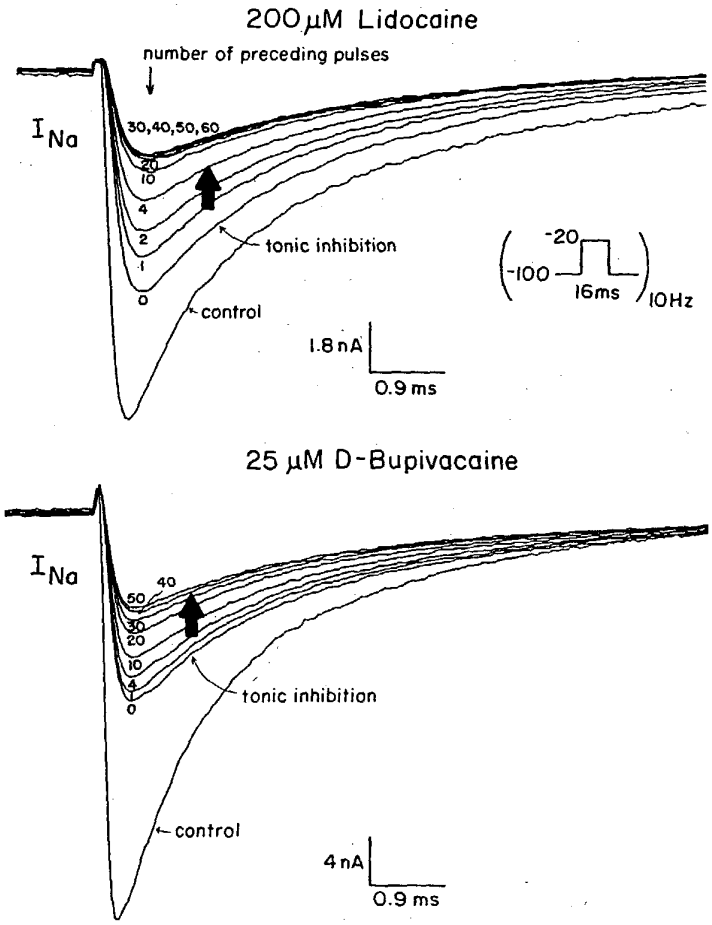

Fig. 15-8. Inhibition of Na^+ currents in myelinated nerves exposed to lidocaine or to bupivacaine. Traces show the inward ionic currents during a 16-millisecond-long depolarization to −20 mV, before drug addition (control), for the first depolarization imposed 5 minutes after beginning drug exposure (0, tonic inhibition), and for the subsequent pulses in a train of depolarizations applied to 10 Hz (identified numerically by their order in the sequence; use-dependent inhibition). T = 13°C. Toad node of Ranvier. (From Chernoff,[38] with permission.)

similar to an inactivated channel; both inactivation and anesthetic binding prevent the conformational changes of the activation process by fully or partially immobilizing the channel.[29] To some extent, blockade of the ion-conducting pore plays a part in channel inhibition, but the contribution from this mechanism seems minor.

Are inactivated channels essential for local anesthetic binding and action? No, because when inactivation is prevented by various chemical reagents or toxins, there is little change in the tonic and phasic actions of local anesthetics.[30] Phasic channel inhibition occurs during depolarizations that are as short as neuronal impulses (1 to 5 ms) because local anesthetics bind more rapidly and with higher affinity to *activated* channels (some open, some in conformations preceding the open state) than to resting channels. During longer depolarizations additional binding to drug-free inactivated channels also can occur[17,25]; this mode of binding probably accounts for much of the therapeutic action of local anesthetic-like class I antiarrhythmics.[31,32]

Regardless of the channel state that binds the drug, by its very binding the local anesthetic stabilizes that state. During phasic block, therefore, more channels become drug-bound during activation, and reciprocally, less activation can occur. Thus, overall binding of anesthetic is increased by channel activation for two reasons: more binding sites become accessible during activation (the "guarded receptor" model)[33] and drug dissociation from activated channels is slower than from resting channels (the *modulated receptor* model).[17]

The specific binding rates and affinities of local anesthetics for the different conformations of the sodium channel depend on the particular drug. When the details of this dependence are correlated with the physicochemical properties of the drug and with the experimental conditions, they provide insight into the nature of the local anesthetic binding site.[3,4]

The Nature of the Local Anesthetic Binding Site

Kinetic and equilibrium measurements of inhibition by diverse local anesthetics reveal much about the binding site. Like the rate of onset of tonic block, the rate of binding for phasic block is greater at more alkaline external pH, which favors the neutral drug in the membrane and both the neutral and cationic species in the cytoplasm.[26] Curiously, cytoplasmic pH has almost no effect on phasic inhibition.[34] Drugs of greater hydrophobicity are proportionately more potent for both tonic and phasic block than less hydrophobic congeners.[3,35,36] However, at equipotent doses of two local anesthetics that differ 100-fold in hydrophobicity and in intrinsic potency (but have very similar pK_as), the rate of phasic binding is almost the same despite the 100-fold difference in their concentrations in solution. The apparent discrepancy between rates and concentrations can be reconciled by postulating that the primary blocking reaction occurs in the membrane phase, where the more potent drug is concentrated by hydrophobic uptake[17,26] (Fig. 15-9).

Dissociation of local anesthetic from the open channel depends little on hydrophobicity, size, pK_a, or external pH. In contrast, drug dissociation from the closed channels depends strongly on all these factors. Dissociation is slightly faster for more hydrophobic compounds,[4,37,38] markedly faster at more alkaline than at neutral external pH,[38,39] and faster for drugs of lower pK_a.[26,37] One simple interpretation of these findings is that anesthetics can leave their blocking site by either a hydrophobic or a hydrophilic pathway.[17] The former accommodates the uncharged base primarily and is 20 to 50 times as fast as the latter, which accommodates the cationic species.

Integrating these physicochemical findings resolves a dynamic picture of local anesthetic action (Fig. 15-9). The binding of tertiary amine compounds occurs primarily from the membrane phase and favors the neutral base species. Dissociation of drug involves primarily the closed conformations of the channel (excitation occurring only briefly) and is slowed by extracellular protons. In brief, hydrophobicity delivers the drug to the receptor and charge keeps it there.[39]

Neurophysiologic Aspects of Phasic Inhibition

Impulse blockade is increased by repetitive stimulation. As the frequency of impulse traffic in an axon is increased, the probability of impulse blockade by local anesthetic also rises. This phenomenon develops along the length of axon exposed to drug, as shown in Figure 15-10. The first impulse to traverse the fiber, where 16 consecutive nodes have been exposed to lidocaine at a concentration that blocks 50 percent of the Na^+ channels at rest, suffers decreasing conduction along the drug-exposed region[40]; yet the reduced impulse still provides enough current at the last anesthetized node to raise the adjacent drug-free region to threshold. Impulse propagation is thus slowed but does not fail. However, the second impulse in the train encounters an exposed region of axon rendered less excitable by the residual phasic inhibition of the first impulse. Action currents at the end of the exposed region are now below the margin of safety and propagation fails.[41] The third impulse propagates down along a path of an even more sharply decreasing excitability. Each subsequent impulse in the train similarly fails to traverse the drugged axon; impulse activity entering the anesthetized region thus maintains its own failure.

An identical phenomenon occurs in vivo. In this situation the frequency of impulses encodes neuronal information (e.g., in sensory fibers the intensity of the physiologic stimulation is encoded in the impulse discharge pattern). Local anesthetics significantly disrupt this pattern, as shown by the example in Figure 15-11 of an afferent Aβ fiber coupled to a slowly adapting mechanoreceptor in the rat's footpad.[41] Application of a subclinical dose of lidocaine to the ensheathed sciatic nerve in vivo leads to a progressive reduction in the average frequency of impulses propagated by one axon, even though the me-

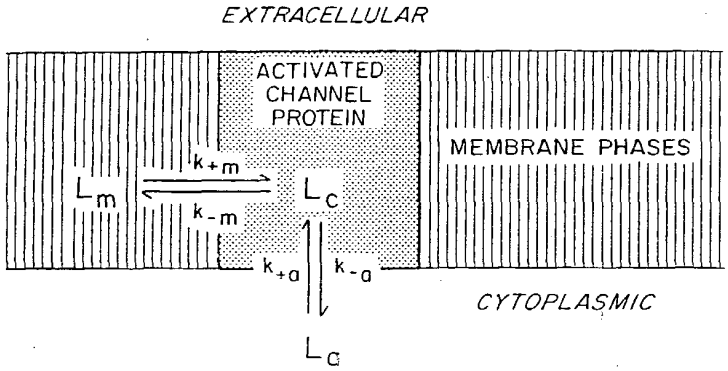

Fig. 15-9. Schematic drawing of drug access routes to a putative local anesthetic binding site on the Na^+ channel. The hydrophilic route, from the cytoplasmic phase, mediates binding of aqueous drug (L_a) directly to the receptor site. The hydrophobic route mediates binding to membrane-associated drug (L_m) to the site. The activated channel (induced by membrane depolarization) binds drug more tightly than the resting channel, but both states of the protein appear to favor the hydrophobic route.

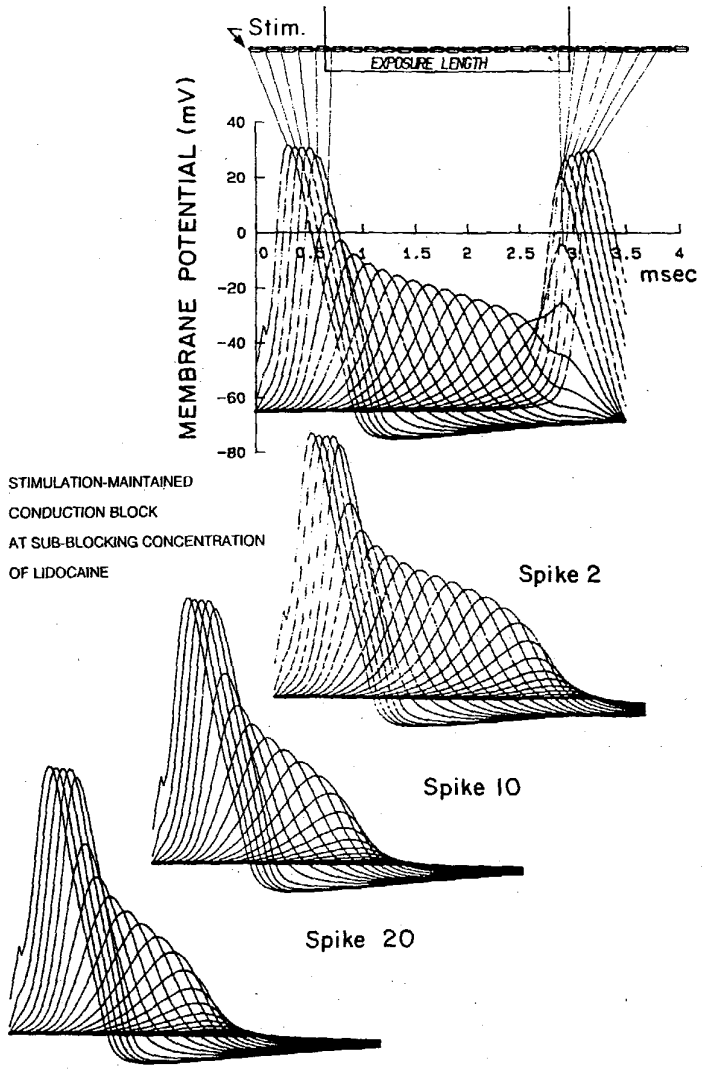

Fig. 15-10. Decremental inhibition of conducted impulses modeled in a myelinated axon shows use-dependent block. In this computer simulation, the membrane potential at each of 26 sequential nodes of Ranvier is plotted as the impulse, stimulated at the leftmost node, propagating to the right. Fifteen nodes in the middle of this fiber are "exposed" to local anesthetics, which reduces both Na^+ and K^+ conductances to tonically inhibited levels (Fig. 15-8) for the first impulse in a train (top frame). Although this impulse's amplitude decrements continuously over the exposed length, local current at the last exposed node is still sufficient to stimulate the next, unexposed node, and conduction continues. Use-dependent drug binding during this spike lowers the Na^+ conductance available for subsequent impulses in the train, which therefore decreases further (compare spike 2 and spike 10) and fail to sustain conduction within the exposed region. (From Raymond et al.,[41] with permission.)

chanical stimulus intensity is increased beyond control level.

Different fiber types in the nerve will be affected differentially by local anesthetics. At the onset of and during recovery from clilnical block, in particular, the longitudinal and radial diffusion of drug will produce concentration variations within and along the nerve.[42] This variation is superimposed on the dynamic use-dependent inhibition to provide variable propagation, which depends on a fiber's geometry, position within the nerve, and functional as well as electrophysiologic properties. No clear relationship has been established between an axon's diameter and its absolute susceptibility to block by local anesthetics, although the temporal sequence of loss of various sensory and sympathetic functions during regional block is well documented.[43,44] For an explanation of the clinical observation, we must look beyond the strictly geometric aspects of an axon. A consideration of fiber functions and physiologic properties may provide a future basis for functionally selective nerve blocks.

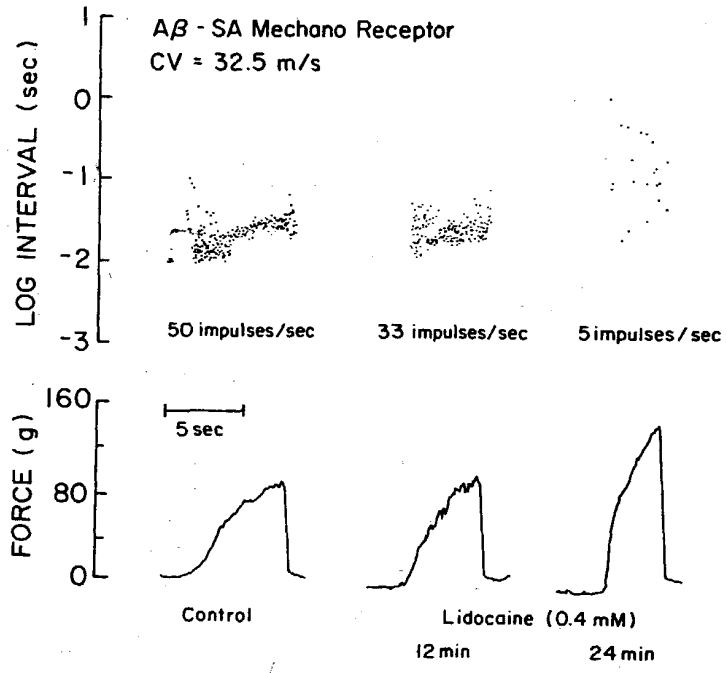

Fig. 15-11. The pattern of impulses in vivo in a cutaneous afferent of the rat is strongly modified by local anesthetic. Discharge frequency (upper traces, shown on a logarithmic scale) in response to increasing pressure on the rat's footpad (lower traces) maintains a relatively constant value (50/s, average) in this slowly adapting mechanoreceptor before drug. Bathing the ensheathed sciatic nerve with lidocaine (0.01 percent over a 2 to 3 cm length) inhibits impulse conduction through the exposed region, so that after 24 minutes of drug exposure, the average frequency has fallen by 90 percent, despite the faster and larger mechanical stimulation. (From Raymond et al.,[41] with permission.)

Summary of Local Anesthetic Mechanisms

Impulse blockade by local anesthetics may be summarized by the following chronology:

1. Solutions of local anesthetic are deposited near the nerve. Diffusion of drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of aminoester anesthetics. The net result is penetration of the nerve sheath by remaining molecules.
2. Local anesthetic molecules then permeate the nerve's axon membranes and equilibrate there and in the axoplasm. The speed and extent of these processes depend on a particular drug's pK_a and the lipophilicity of its base and cation species.
3. Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting conformational changes that underlie channel activation.
4. During onset of and recovery from local anesthesia, impulse blockade is incomplete and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional, use-dependent binding to Na^+ channels.
5. One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions. The access to this site may potentially involve multiple pathways, but for clinical local anesthetics the primary route is the hydrophobic approach from within the axon membrane.
6. The clinically observed rates of onset of and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecules into and out of the nerve, not by their much faster binding and dissociation to ion channels.

CLINICAL PHARMACOLOGY

The successful use of regional anesthesia requires knowledge of the pharmacologic properties of the various local anesthetic drugs, as well as technical skill in the performance of the nerve block. Local anesthetic requirements vary considerably, depending on factors such as type of block, surgical procedure, and physiologic status of the patient.

The clinically useful aminoester local anesthetics are procaine, chloroprocaine, and tetracaine. The amino amides consist of lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, locus of biotransformation, and allergic potential. Amides are extremely stable, while esters are relatively unstable in solution. The aminoesters are hydrolyzed in plasma by the cholinesterase enzymes, whereas the

amide compounds undergo enzymatic degradation in the liver. *p*-Aminobenzoic acid is one of the metabolites of ester-type compounds that can induce allergic-type reactions in a small percentage of patients. The aminoamides are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

General Considerations

The clinically important properties of the various local anesthetics include potency, speed of onset, duration of anesthetic action, and differential sensory/motor blockade. As previously indicated, the profile of the individual drugs is determined by their physicochemical characteristics (Table 15-2).

Anesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency,[5,35,45,46] since the anesthetic molecule must penetrate into the nerve membrane. Clinically, however, the correlation between hydrophobicity and anesthetic potency is not as precise as in an isolated nerve. Lidocaine is approximately twice as potent as prilocaine in an isolated preparation,[47] but in humans little difference in anesthetic potency is apparent between these agents.[48] Similarly, etidocaine is more potent than bupivacaine in an isolated nerve, whereas clinically etidocaine is actually less active than bupivacaine.[46,49,50] The difference between in vitro and in vivo results is related to a number of factors such as the vasodilator or tissue redistribution properties of the various local anesthetics. For example, lidocaine causes a greater degree of vasodilation than prilocaine, resulting in its more rapid vascular uptake so that fewer lidocaine molecules are available for neural blockade.[51] The extremely high lipid solubility of etidocaine may result in a greater uptake of this agent by adipose tissue, such as in the epidural space, which again results in fewer molecules available for neural blockade as compared with bupivacaine.

Onset of Action

The onset of conduction block in isolated nerves is related to the physicochemical properties of the individual agents. In vivo latency is also dependent on the dose or concentration of local anesthetic employed. For example, 0.25 percent bupivacaine possesses a rather slow onset of action. However, increasing the concentration to 0.75 percent results in a significant acceleration of anesthetic effect.[50] Chloroprocaine demonstrates a rapid onset of action in humans despite the facts that its pK_a is approximately 9 and its onset of action in isolated nerves is relatively slow.[52] However, the low systemic toxicity of this agent allows its use in high concentrations (e.g., 3 percent). Therefore, the rapid onset in vivo of chloroprocaine may be related simply to the large number of molecules placed in the vicinity of peripheral nerves. In humans, 1.5 percent lidocaine produced a more rapid onset of epidural anesthesia than 1.5 percent chloroprocaine[53]; however, 3 percent chloroprocaine resulted in a more rapid onset than 2.0 percent lidocaine.

Duration of Action

The duration of action of the various local anesthetics differs markedly. Procaine and chloroprocaine demonstrate a short duration of action. Lidocaine, mepivacaine, and prilocaine produce a moderate duration of anesthesia, while tetracaine, bupivacaine, and etidocaine have the longest durations. For example, with procaine the duration of brachial plexus blockade is 30 to 60 minutes, while up to approximately 10 hours of anesthesia have been reported following use of bupivacaine or etidocaine for brachial plexus blockade.[54]

In humans the duration of anesthesia is markedly influenced by the peripheral vascular effects of the local anesthetic drugs. All local anesthetics except cocaine tend to have a biphasic effect on vascular smooth muscle. At low concentrations these agents tend to cause vasoconstriction, whereas at clinically employed concentrations they cause vasodilation.[55,56] However, differences exist in the degree of vasodilator activity produced by the various drugs. For example, lidocaine is a more potent vasodilator than mepivacaine or prilocaine. Although little difference in the duration of conduction block is apparent between these agents in an isolated nerve, in vivo the anesthesia produced by lidocaine is of shorter duration than that produced by mepivacaine or prilocaine.

Differential Sensory/Motor Blockade

Another important clinical consideration is the ability of local anesthetic agents to cause a differential inhibition of sensory and motor activity. Bupivacaine is the most useful agent in terms of producing adequate antinociception without profound inhibition of motor activity regardless of the regional anesthetic technique employed. Bupivacaine and etidocaine provide an interesting contrast in their differential sensory and motor blocking activity, although they are both potent, long-acting anesthetics[57] (Fig. 15-12). Bupivacaine is widely used epidurally for obstetric analgesia and postoperative pain management because it can provide analgesia with only mild muscle weakness, particularly when used in concentrations of 0.125 percent or less (also see Ch. 61).

Traditional texts often state that small-diameter axons, such as C fibers, are more susceptible to local anesthetic block than are larger-diameter fibers. However, when careful measurements are made of single impulse annihilation in individual nerve fibers, no such differential susceptibility is seen.[58,59] Repetitive stimulation, such as occurs during propagation of trains of impulses, the normal mode of operation for neuronal information passage (Fig. 15-11), produces a further, phasic inhibition of excitability, but it is unclear how this will effect a functionally selective failure of impulses. The length of drug-exposed nerve in the intrathecal space, because of anatomic restrictions can explain clinically documented differential spinal or epidural blockade,[42] since longer drug-exposed regions yield block by lower concentrations of local anesthetic.[40]

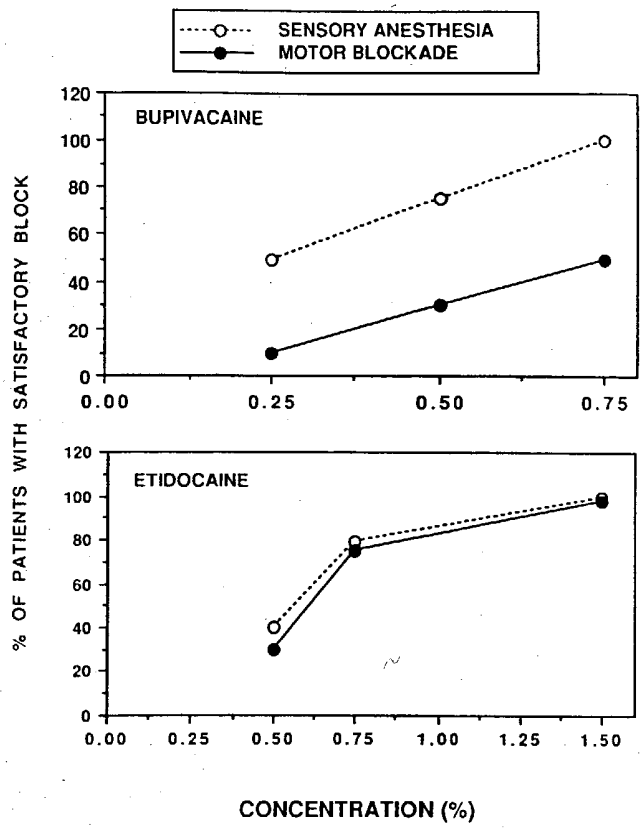

Fig. 15-12. Comparative inhibition of sensory and motor activity following the epidural administration of varying concentrations of bupivacaine and etidocaine.

However, this reasoning does not explain the functionally differential loss from peripheral nerve block. Other factors may include the actual spread of the drug along the nerve[60] or its selective ability to inhibit Na^+ channels over K^+ channels,[61] which in itself can produce a differential block because these channels are present in very different proportions in different types of nerves.[62]

Factors Influencing Anesthetic Activity in Humans

Dosage of Local Anesthetic

As the dosage of local anesthetic is increased, the probability and duration of satisfactory anesthesia increases and the time to onset of block is shortened. The dosage of local anesthetic can be increased by administering either a larger volume or a more concentrated solution. For example, increasing the concentration of epidurally administered bupivacaine from 0.125 to 0.5 percent while maintaining the same volume of injectate (10 ml) resulted in shorter latency, improved incidence of satisfactory analgesia, and longer duration of sensory analgesia.[63] Similarly, an increase in the concentration of epidural bupivacaine in surgical patients from 0.5 to 0.75 percent with a concomitant increase in dosage from approximately 100 to 150 mg produced a more rapid onset and prolonged sensory anesthesia, a greater frequency of satisfactory sensory anesthesia, and more profound motor blockade[50] (Fig. 15-12). Prilocaine (600 mg), administered epidurally either as 30 ml of a 2 percent solution or 20 ml of a 3 percent solution, showed no difference in onset time, adequacy, or duration of anesthesia and onset time, depth, and duration of motor blockade.[48] The volume of anesthetic solution probably influences the spread of anesthesia. For example, 30 ml of 1 percent lidocaine administered into the epidural space produced a level of anesthesia that was 4.3 dermatomes higher than that achieved when 10 ml of 3 percent lidocaine was given.[64]

Addition of Vasoconstrictors

Vasoconstrictors, usually epinephrine (5 μ/ml), are frequently included in local anesthetic solutions to decrease the rate of vascular absorption, thereby allowing more anesthetic molecules to reach the nerve membrane and so improve the depth and duration of anesthesia, and also to provide a marker for inadvertent intravascular injection.[65] Epinephrine in a concentration of 1 : 200,000 has been reported to provide the optimal degree of vasoconstriction when employed with lidocaine for epidural or intercostal use.[60] Other vasoconstrictor agents such as norepinephrine and phenylephrine have been used but do not appear to be superior to epinephrine. For example, equipotent concentrations of epinephrine and phenylephrine prolong the duration of spinal anesthesia produced by tetracaine to a similar extent.[66]

The extent to which epinephrine prolongs the duration of anesthesia depends on the specific local anesthetic employed and the site of injection. Epinephrine will significantly extend the duration of both infiltration anesthesia and peripheral nerve blocks with many agents.[67,68] Epinephrine does not markedly prolong the duration of motor blockade by epidural bupivacaine or etidocaine; however, it does extend sensory blockade by these epidural agents.[57] The depth and duration of epidural analgesia in obstetric patients was improved slightly when epinephrine 1 : 300 : 000 was added to 0.25 percent bupivacaine.[69] α-Adrenergic receptors in the spinal cord are known to mediate endogenous analgesic mechanisms,[70] and the increased depth of analgesic action produced by epinephrine with both epidural and intrathecal local anesthetics may arise both from this pharmacodynamic mechanism and from the pharmacokinetic (vasoconstrictive) action.

Site of Injection

The most rapid onset but the shortest duration of action occurs following intrathecal or subcutaneous administration of local anesthetics. The longest latencies and durations are observed following brachial plexus blocks. For example, intrathecal bupivacaine usually will produce anesthesia within 5 minutes that will persist for 3 to 4 hours. However, when bupivacaine is administered for brachial plexus blockade, the onset time is approximately 20 to 30 minutes, while the duration of anesthesia averages 10 hours. These differences in the onset and duration of anesthesia are due in part to the particu-

lar anatomy of the area of injection. This will influence the rates of diffusion and vascular absorption, which in turn affect the amount of drug employed for various types of regional anesthesia. In the subarachnoid space, for example, the lack of a nerve sheath around the spinal cord and the deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action, while the relatively small amount of drug employed for spinal anesthesia probably accounts for the short duration of conduction block.

On the other hand, the onset of brachial plexus blockade is slow, since the anesthetic agent is usually deposited at some distance from the nerve roots and must diffuse through various tissue barriers before reaching the nerve membrane. The prolonged blockade is probably related to the decreased rate of vascular absorption from that site and the larger doses of drug required for this regional anesthetic technique.

Carbonation and pH Adjustment of Local Anesthetics

The presence of bicarbonate carbon dioxide in a solution of local anesthetic applied to an isolated nerve results in a more rapid onset and a decrease in the minimum concentration (Cm) required for conduction blockade.[71-73] Although the effect of carbon dioxide on local anesthetic activity is easily demonstrable in isolated nerve,[71,72] controversy exists concerning the clinical utility of carbonated local anesthetic solutions. For example, some studies have failed to demonstrate a significantly more rapid onset of action for lidocaine carbonate as compared with lidocaine hydrochloride for epidural blockade,[74] while others have reported a significant reduction in onset time of epidural blockade with lidocaine carbonate.[75] Similar discrepancies existed when bupivacaine hydrochloride and bupivacaine carbonate were evaluated clinically.[76,77] Although the effect of carbon dioxide on the latency of conduction blockade may be controversial, carbonated solutions appear to improve the depth of sensory and motor blockade when administered into the epidural space.[74,75] In addition, these solutions may produce a more complete blockade of the radial, median, and ulnar nerves when employed for brachial plexus blockade.[78]

Addition of sodium bicarbonate to local anesthetic solutions has also been reported to decrease the onset time of conduction blockade.[78,79] An increase in the pH of the local anesthetic solution increases the amount of drug in the uncharged base form, which should enhance the rate of diffusion across the nerve sheath and nerve membrane, resulting in a more rapid onset of anesthesia. Alkalinization of solutions of bupivacaine or lidocaine reportedly did significantly decrease the latency period of brachial plexus and epidural blockade.[78,79] On the other hand, at least one study failed to demonstrate an improved onset of brachial plexus blockade when the pH of bupivacaine solution was increased by addition of sodium bicarbonate.[80]

Studies on isolated, desheathed nerves using a variety of impulse blocking agents at constant extracellular pH have shown that un-ionized anesthetics (e.g., benzocaine) as well as ionizable tertiary amines are potentiated by bicarbonate carbon dioxide buffers.[73] The potency of cationic local anesthetics was unaffected by bicarbonate carbon dioxide. Therefore, the mechanism of "ion trapping," whereby the ionized form of the drug is concentrated in the axoplasm by the internal acidification wrought by membrane-permeant carbon dioxide molecules, does not fully account for potentiation by bicarbonate/carbon dioxide. Furthermore, this potentiation in isolated, desheathed nerve is strongly dependent on bicarbonate concentration but almost independent of carbon dioxide tension (PCO_2). At present there is no easy explanation for the potentiation of local anesthetics by bicarbonate buffers, nor has a clear connection been established between in vitro results and the clinical phenomena.

Mixtures of Local Anesthetics

The use of mixtures of local anesthetics for regional anesthesia has become relatively popular in recent years. The basis for this practice is to compensate for the short duration of action of certain agents such as chloroprocaine and lidocaine and the long latency of other agents such as tetracaine and bupivacaine. Mixtures of chloroprocaine and bupivacaine theoretically should offer significant clinical advantages owing to the rapid onset and low systemic toxicity of chloroprocaine and the long duration of action of bupivacaine. A mixture of 3 percent chloroprocaine and 0.5 percent bupivacaine was reported to produce a short latency and prolonged duration of brachial plexus blockade.[81] However, subsequent studies indicated that the duration of epidural anesthesia produced by a mixture of chloroprocaine and bupivacaine was significantly shorter than that obtained with bupivacaine alone, while time to onset was longer than that of chloroprocaine alone.[82] Isolated nerve studies suggest that a metabolite of chloroprocaine may inhibit the binding of bupivacaine to membrane sites.[83] At present there do not appear to be any clinically significant advantages to the use of mixtures of local anesthetic agents. Etidocaine and bupivacaine provide clinically acceptable onsets of action and prolonged durations of anesthesia. In addition, the use of catheter techniques for many forms of regional anesthesia makes it possible to indefinitely extend the duration of action of rapidly acting agents such as chloroprocaine or lidocaine.

Pregnancy (Also See Ch. 61)

The spread and depth of epidural and spinal anesthesia are reported to be greater in pregnant than in nonpregnant women.[84] This was originally attributed to mechanical factors associated with pregnancy — that is, dilated epidural veins decrease the diameter of the epidural and subarachnoid space. Hormonal alterations may also play a role in the apparent increase in local anesthetic sensitivity during pregnancy, since a greater spread of epidural anesthesia occurs during the first trimester of pregnancy, preceding any gross change in vascular dimensions within the epidural or subarachnoid spaces.[85] A correlation appears to exist between progesterone levels in cerebrospinal fluid and the milligrams per segment requirement of lidocaine for spinal anesthesia in pregnant and non-

pregnant patients.[86] Isolated nerve studies have shown a more rapid onset and an increased sensitivity to local anesthetic-induced conduction blockade in vagus nerves obtained from pregnant rabbits as compared with nonpregnant controls.[87,88] These results suggest that hormonal changes associated with pregnancy enhance the apparent potency of local anesthetics; thus, the dosage probably should be reduced in patients in all stages of pregnancy.

CHOICE OF LOCAL ANESTHETIC FOR VARIOUS REGIONAL ANESTHETIC PROCEDURES (Also See Chs. 46 to 48, 73, and 74)

On the basis of anatomic considerations, regional anesthesia may be divided into infiltration anesthesia, intravenous regional anesthesia, peripheral nerve blockade, central neural blockade, and topical anesthesia.

Infiltration Anesthesia

Any local anesthesia may be employed for infiltration anesthesia. Onset of action is almost immediate for all agents following intradermal or subcutaneous administration; however, duration of anesthesia varies (Table 15-4). Epinephrine will markedly prolong the duration of infiltration anesthesia by all local anesthetic drugs. This effect is most pronounced when epinephrine is added to lidocaine. Choice of a specific drug for infiltration anesthesia basically depends on the desired duration of action.

The dosage of local anesthetic required for adequate infiltration anesthesia depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure. When large surface areas have to be anesthetized, large volumes of dilute anesthetic solutions should be used.

Patients frequently experience pain immediately after subcutaneous injection of local anesthetic solutions.[89] This is due in part to the acidic nature of these solutions.[90,91] In addition, certain agents such as etidocaine are associated with a greater frequency and intensity of pain, while lidocaine is perceived as less painful.[6,90]

Intravenous Regional Anesthesia

Intravenous regional anesthesia involves intravenous administration of a local anesthetic into a tourniquet-occluded limb. The local anesthetic diffuses from the peripheral vascular bed to nonvascular tissue such as axons and nerve endings. Both the safety and efficacy of this regional anesthetic procedure depend on the interruption of blood flow to the involved limb. Intravenous regional anesthesia has been used primarily for surgical procedures on the upper limbs. Shorter procedures on the foot can also be successfully performed under intravenous regional anesthesia. Here the tourniquet should be applied just below the fibular neck to avoid pressure over the superficial peroneal nerve.

Lidocaine has been the drug most frequently used for intravenous regional anesthesia and is the only drug officially approved by the Food and Drug Administration for intravenous regional anesthesia in the United States. Prilocaine, mepivacaine, chloroprocaine, procaine, bupivacaine, and etidocaine have also been used successfully; however, thrombophlebitis has been reported in several patients in whom chloroprocaine was used.[92] Cardiovascular collapse has been reported following the use of bupivacaine for intravenous regional anesthesia, and this use of bupivacaine is not recommended in the United States.[93]

In general, approximately 3 mg/kg (40 ml of 0.5 percent solution) of preservative-free lidocaine without epinephrine is used for upper extremity procedures. For surgical procedures on the lower limbs, 50 to 100 ml of 0.25 percent lidocaine has been used.

Table 15-4. Infiltration Anesthesia

Drug	Concentration (%)	Plain Solution		Epinephrine-Containing Solution	
		Max Dose (mg)	Duration (min)	Max Dose (mg)	Duration (min)
Short duration					
Procaine					
Chloroprocaine	1.0-2.0	800	15-30	1,000	30-90
Moderate duration					
Lidocaine	0.5-1.0	300	30-60	500	120-360
Mepivacaine	0.5-1.0	300	45-90	500	120-360
Prilocaine	0.5-1.0	500	30-90	600	120-360
Long duration					
Bupivacaine	0.25-0.5	175	120-240	225	180-420
Etidocaine	0.5-1.0	300	120-180	400	180-420

Table 15-5. Minor Nerve Blocks (Also See Ch. 47)

Drug	Usual Concentration (%)	Plain Solutions: Usual Volume (ml)	Plain Solutions: Dosage (mg)	Plain Solutions: Average Duration (min)	Epinephrine-Containing Solutions: Average Duration (min)
Procaine, Chloroprocaine	2	5-20	100-400	15-30	30-60
Lidocaine, Mepivacaine, Prilocaine	1	5-20	50-200	60-120	120-180
Bupivacaine	0.25	5-20	12.5-50	180-360	240-480
Etidocaine	0.5	5-20	25-100	120-240	180-420

Peripheral Nerve Blockade (Also See Chs. 47 and 48)

Regional anesthetic procedures that inhibit conduction in fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade. This form of regional anesthesia has been subdivided arbitrarily into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities such as the ulnar or radial nerve, while major nerve blocks involve the blocking of two or more distinct nerves or a nerve plexus.

Most local anesthetic drugs can be used for minor nerve blocks. The onset of block is rapid with most drugs, and the choice of drug is determined primarily by the required duration of anesthesia. A classification of the various drugs according to their duration of action is shown in Table 15-5. The duration of both sensory analgesia and motor blockade is prolonged significantly when epinephrine is added to the various local anesthetic solutions.

In 1986 a technique of intrapleural regional analgesia was described as an alternative to multiple intercostal nerve blocks.[94] This procedure involves administration of local anesthetic solution into the pleural space. An epidural needle is inserted into the pleural space, usually by way of the fourth to the ninth intercostal space. An epidural catheter is then passed into the pleural space approximately 5 cm beyond the tip of the needle. The needle is removed, and the local anesthetic is administered through the catheter. This technique has proved useful for unilateral postoperative analgesia following cholecystectomies, mastectomies, and nephrectomies,[95,96] but its efficacy for post-thoracotomy pain is controversial.[97] Most frequently, 22 to 30 ml of 0.5 percent bupivacaine with epinephrine has been employed in this technique; the duration of analgesia averages approximately 8 hours with a range of 4 to 24 hours. The advantage of the technique is the ability to administer subsequent injections of local anesthetics via catheter to provide long-lasting analgesia without subjecting patients to repeated multiple intercostal nerve blocks. This technique has been associated with extremely high plasma concentrations of anesthetic.[94]

Brachial plexus blockade for upper limb surgery is the most common major peripheral nerve block technique. A significant difference exists between the onset times of various agents when these blocks are used (Table 15-6). In general, the agents of intermediate potency exhibit a more rapid onset than the more potent compounds. Onset times of approximately 14 minutes for lidocaine and mepivacaine have been reported, as compared with mean latency values of approximately 23 minutes for bupivacaine.[99] Etidocaine may be an exception, since it produces a relatively rapid onset and a long duration of block.

Epinephrine will prolong the duration of most local anes-

Table 15-6. Major Nerve Blocks (Also See Ch. 47)

Drug w/Epinephrine 1:200,000	Usual Concentration (%)	Usual Volume (ml)	Maximal Dose (mg)	Usual Onset (min)	Usual Duration (min)
Lidocaine	1-1.5	30-50	500	10-20	120-240
Mepivacaine	1-1.5	30-50	500	10-20	180-300
Prilocaine	1-2	30-50	600	10-20	180-300
Bupivacaine	0.25-0.5	30-50	225	15-30	360-720
Etidocaine	0.5-1.0	30-50	400	10-20	360-720
Tetracaine	0.25-0.5	30-50	200	20-30	300-600

thetics employed for brachial plexus blockade, but is less effective with drugs having intrinsically longer durations of action. The variation in duration of anesthesia after brachial plexus blockade is also considerably greater than that observed with other types of conduction block. For example, durations of anesthesia varying from 4 to 30 hours have been reported for bupivacaine. It would be prudent to forewarn patients about to be given a major nerve block about the possibility of prolonged sensory and motor block in the involved region, particularly when agents such as bupivacaine and etidocaine are employed.

Central Neural Blockade (Also See Ch. 46)

Any of the local anesthetic drugs may be used for epidural anesthesia (Table 15-7), although procaine and tetracaine are rarely used owing to their long onset times. The drugs of intermediate potency produce surgical anesthesia of 1 to 2 hours duration, whereas the long-acting drugs usually produce 3 to 5 hours of anesthesia. The duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), while the long-acting drugs benefit little from its addition. Onset of lumbar epidural anesthesia occurs within 5 to 15 minutes following administration of chloroprocaine, lidocaine, mepivacaine, prilocaine, and etidocaine. Bupivacaine has a slower onset of action.

Bupivacaine at 0.25 and 0.5 percent produces adequate analgesia with minimal motor deficit. These solutions of bupivacaine are useful for obstetric epidural analgesia and postoperative analgesia. Bupivacaine at 0.75 percent is associated with a more profound degree of motor block, which makes this solution most suitable for major surgical procedures. Etidocaine produces adequate sensory analgesia and profound motor block and is primarily useful for surgical procedures in which muscle relaxation is required.

Drugs available for subarachnoid administration are shown in Table 15-8. Tetracaine, which is the most commonly used spinal agent in the United States, is available both as crystals and as a 1 percent solution, which may be diluted with 10 percent glucose to obtain a 0.5 percent hyperbaric solution.

Hypobaric solutions of tetracaine (tetracaine in sterile water) may be used for specific operative situation, for example, anorectal or hip surgery. Isobaric tetracaine obtained by mixing 1 percent tetracaine with cerebrospinal fluid or normal saline is particularly useful for lower limb surgical procedures. In recent years bupivacaine has been introduced as a spinal anesthetic, which is prepared as a hyperbaric solution at a concentration of 0.75 percent with 8.25 percent dextrose. A 0.5 percent isobaric solution of bupivacaine is also available in some countries.

Intrathecal bupivacaine possesses an anesthetic profile similar to that of tetracaine.[100,101] However, differences do exist between the two drugs. Although two-segment regression of anesthesia is similar for bupivacaine and tetracaine, the total duration of sensory anesthesia is significantly longer following the subarachnoid administration of tetracaine. The depth and duration of motor blockade are also greater with tetracaine than with bupivacaine. On the other hand, bupivacaine has been reported in some studies to be associated with less hypotension than tetracaine. In addition, the frequency of tourniquet pain in the lower limbs during certain orthopedic surgical procedures has been reported to be significantly reduced when bupivacaine instead of tetracaine is employed for spinal anesthesia.[102,103]

Lidocaine provides a short duration of spinal anesthesia, where tetracaine and bupivacaine are considered to be agents of long duration. Onset of spinal anesthesia is extremely rapid with a drug such as lidocaine. The addition of vasoconstrictors may prolong the duration of spinal anesthesia: for example, addition of 0.2 to 0.3 mg of epinephrine to tetracaine solutions will produce a 50 percent or greater increase in duration. The duration of spinal anesthesia produced by tetracaine can also be increased to a similar extent by adding 1 to 5 mg of phenylephrine. The addition of epinephrine to bupivacaine or lidocaine may not significantly prolong the duration of spinal anesthesia in thoracic segments,[104,105] although the total duration of anesthesia (e.g., in the lumbosacral roots) will be significantly increased.

Topical Anesthesia

A number of local anesthetic formulations are available for topical anesthesia (Table 15-9), lidocaine, dibucaine, tetracaine, and benzocaine being the drugs most commonly employed. In general, these preparations provide effective but

Table 15-7. Epidural Anesthesia (Also See Ch. 46)

Drug w/Epinephrine 1:200,000	Usual Concentration (%)	Usual Volume (ml)	Total Dose (mg)	Usual Onset (min)	Usual Duration (min)
Chloroprocaine	2-3	15-30	300-900	5-15	30-90
Lidocaine	1-2	15-30	150-500	5-15	60-180
Mepivacaine	1-2	15-30	150-500	5-15	
Prilocaine	1-3	15-30	150-600	5-15	180-300
Bupivacaine	0.25-0.75	15-30	37.5-225	10-20	
Etidocaine	1.0-1.5	15-30	150-300	5-15	

REGIONAL BLOCKADE

In Clinical Anesthesia and Management of Pain

THIRD EDITION

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pain-free and still be able to move her legs, which is one of the primary reasons why this agent has enjoyed popularity for continuous epidural blockade during labor. Increasing the concentration of bupivacaine to 0.75% will increase the depth of both sensory and motor blockade while also shortening latency and producing a more prolonged duration of anesthesia.[131] Etidocaine, on the other hand, shows little separation between sensory and motor blockade. To achieve adequate epidural sensory anesthesia, 1.5% concentrations of etidocaine are usually required. At these concentrations, etidocaine has an extremely rapid onset of action and a prolonged duration of anesthesia; however, sensory anesthesia is associated with a profound degree of motor blockade. Thus etidocaine is a valuable agent, particularly for epidural blockade in surgical situations in which optimum muscle relaxation is desirable, because it combines a rapid onset, prolonged duration, and satisfactory quality of anesthesia with profound motor blockade. This marked effect on motor function renders etidocaine of limited value, however, for obstetric analgesia and postoperative pain relief.

NONPHARMACOLOGIC FACTORS INFLUENCING ANESTHETIC ACTIVITY

Although the inherent pharmacologic properties of the various local anesthetic agents will basically determine their anesthetic profile, other factors may influence the quality of regional anesthesia, including (i) dosage of local anesthetic administered; (ii) addition of a vasoconstrictor to the local anesthetic solution; (iii) site of administration; (iv) use of additives; and (v) mixtures of local anesthetic solutions.

Dosage of Local Anesthetic Solutions

The mass of drug administered will influence the onset, potency, and duration of anesthesia (Table 4-2).[21] As the dose of local anesthetic is increased, the frequency of satisfactory anesthesia and the duration of anesthesia will increase and the time for onset of anesthesia will decrease. In general, the dosage of local anesthetic administered can be increased by administering a larger volume of a less concentrated solution or a smaller volume of a more concentrated solution. In clinical practice, however, an increase in dosage is usually achieved by using a more concentrated solution of the specific agent. For example, a dose-response study involving the use of bupivacaine for epidural analgesia in women in labor showed that increasing the concentration from 0.125% to 0.5% while maintaining the same volume of injectate (10 ml) resulted in a decreased latency, improved incidence of satisfactory analgesia, and an increased duration of sensory analgesia.[92] A similar study involving the use of bupivacaine for surgical anesthesia also demonstrated that increasing the concentration from 0.5% to 0.75% with a concomitant increase in dosage from about 100 mg to 150 mg produced a more rapid onset and prolonged duration of sensory anesthesia.[131] In addition, the frequency of satisfactory sensory anesthesia was increased and the depth of motor blockade enhanced. The relative influence of volume, concentration, and dosage was demonstrated in a study in which prilocaine (600 mg) administered epidurally either as 30 ml of a 2% solution or 20 ml of 3% solution was evaluated.[41] No difference in onset, adequacy, or duration of anesthesia and onset, depth, and duration of motor blockade was observed despite differences in volume and concentration of anesthetic solution used, since the dosage was maintained constant. The volume of anesthetic solution administered may influence the spread of anesthesia; for example, 30 ml of 1% lidocaine administered into the epidural space was shown to produce a level of anesthesia that was 4.3 dermatomes higher than that achieved when 10 ml of 3% lidocaine was used.[52] Thus, except for the possible effect on the spread of anesthesia, the primary qualities of regional anesthesia, namely, onset, depth, and duration of blockade, are related to the mass of drug injected, that is, the product of volume times concentration.

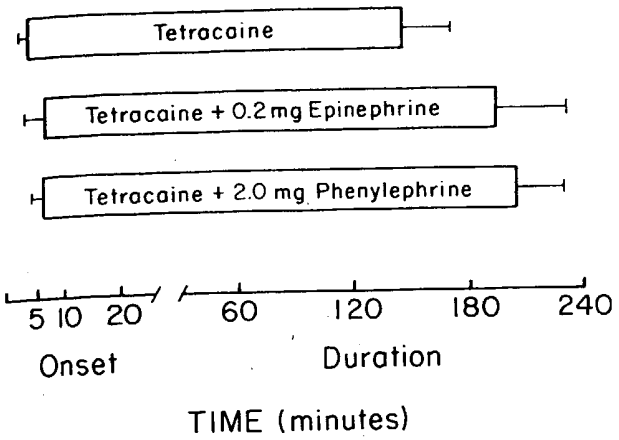
TABLE 4-2. *Effects of dose and epinephrine on local anesthetic properties*

	Increased dose (concentration or volume)	Addition of epinephrine
Onset time	↓	↓[a]
Degree of motor blockade	↑	↑
Degree of sensory blockade	↑	↑
Duration of blockade	↑	↑
Area of blockade	↑	↑
Peak plasma concentration	↑	↓

[a] Minimal effect for etidocaine.

Addition of a Vasoconstrictor to Local Anesthetic Solutions

Vasoconstrictors, particularly epinephrine, are frequently added to local anesthetic solutions. The decrease in the rate of vascular absorption that results from adding epinephrine will allow more anesthetic molecules to reach the nerve membrane, thereby improving the depth and duration of anesthesia (Table 4-2). Local anesthetic solutions usually contain a 1:200,000 (5 μg/ml) concentration of epinephrine, a concentration that has been reported to provide an optimal degree of vasoconstriction when used with lidocaine for epidural or intercostal use.[13] Little information is available on the optimum concentration of epinephrine when used with other local anesthetic agents. Other vasoconstrictor agents such as norepinephrine and phenylephrine have been used as additives to solutions of local anesthetics. Regional blood flow studies indicate that epinephrine is more effective as a vasoconstrictor than norepinephrine when combined with local anesthetic agents.[46] Phenylephrine has been re-



IG. 4-4. Comparative effect of epinephrine and phenylephrine on the duration of spinal anesthesia produced by tetracaine. (Data derived from Concepcion, M., Maddi, R., Francis, D., *et al.*: Vasoconstrictors in spinal anesthesia with tetracaine. A comparison of epinephrine and phenylephrine. Anesth. Analg., *63*:134, 1984.)

ported to produce the greatest prolongation of spinal anesthesia when combined with tetracaine[102]; however, more recent studies conducted under double-blind conditions indicated that at equipotent doses no differences existed between the ability of epinephrine and phenylephrine to prolong the duration of spinal anesthesia produced by tetracaine (Fig. 4-4).[37]

Differences exist in terms of the effect of epinephrine in prolonging the duration of action of various local anesthetic agents. Procaine, lidocaine, and mepivacaine, for example, benefit greatly from the addition of epinephrine in terms of prolonging the duration of infiltration anesthesia, peripheral nerve blocks, and epidural blockade.[2,19,64,141] The duration of action of prilocaine, bupivacaine, and etidocaine is also prolonged by adding epinephrine when these agents are used for infiltration and peripheral nerve blocks.[2,97,141] The duration of action of these agents is not, however, markedly affected by epinephrine following epidural blockade.[19,26,83] The decreased vasodilator action of prilocaine compared to that of lidocaine is believed responsible for the reduced effect of added epinephrine to solutions of prilocaine. With bupivacaine and etidocaine, the high lipid solubility of these agents may be responsible for the diminished effect of epinephrine. These agents are taken up substantially by epidural fat and then slowly released, which contributes to their prolonged duration of action; however, the interaction of epinephrine and the long-acting agents, such as bupivacaine, is dependent on the concentration of drug used. In epidural blockade for labor, for example, the frequency and the duration of adequate analgesia were improved when epinephrine 1:200,000 was added to 0.125% and 0.25% bupivacaine[92]; however, the addition of epinephrine to 0.5% and 0.75% bupivacaine was not associated with a significant improvement in the frequency of satisfactory epidural blockade in obstetric or surgical patients.[92,134] The degree of motor blockade is enhanced following the epidural administration of epinephrine-containing solutions of bupivacaine and etidocaine.[134] The differential effect of epinephrine in terms of prolonging the duration of action of local anesthetic agents is most apparent in the subarachnoid space. Epinephrine significantly extends the duration of spinal anesthesia when combined with tetracaine.[7,37] The duration of effective surgical anesthesia is not, however, markedly enhanced when solutions of lidocaine or bupivacaine with epinephrine are administered intrathecally.[31,32]

Site of Injection

The site of administration of local anesthetic agents will influence their anesthetic profile. Although local anesthetics are frequently classified as agents of short, moderate, or long duration with a slow or rapid onset of action, these general properties are influenced by the type of anesthetic procedure performed. Tetracaine, for example, is usually considered an agent of slow onset and long duration, but its onset of action is quite rapid (about 3 min) when administered intrathecally, whereas the duration of spinal anesthesia with tetracaine is only 2 to 3 hours.[37] In terms of latency, the most rapid onset of action occurs after the intrathecal or subcutaneous administration of local anesthetics, whereas the slowest onset times are observed during the performance of brachial plexus blocks.[40] With regard to the duration of anesthesia, an agent such as bupivacaine possesses a duration of surgical anesthesia of about 4 hours when administered into the epidural space (Fig. 4-5). When bupivacaine is administered for brachial plexus blockade, however, the duration of anesthesia averages 10 hours. Differences in the onset and the duration of anesthesia depending on the site of injection are partly due to the particular anatomy of the area of injection, the variation in the rate of vascular absorption, and the amount of drug used for various types of regional anesthesia. In the case of spinal anesthesia, the lack of a nerve sheath around the spinal cord and the deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action. On the other hand, the relatively small amount of drug used for spinal anesthesia probably accounts for the relatively short duration of action associated with this particular technique. With brachial plexus blockade, the onset of anesthesia is slow due to the anesthetic agent usually being deposited at some distance from the nerve roots, and therefore time for diffusion to the nerve membrane is required before signs of anesthesia are apparent. The long duration of brachial plexus blockade observed with most local anesthetics but, in particular, with the longer-acting agents is probably related to the decreased rate of vascular absorption from that site, and also the larger doses of drug commonly used for this regional anesthetic technique.

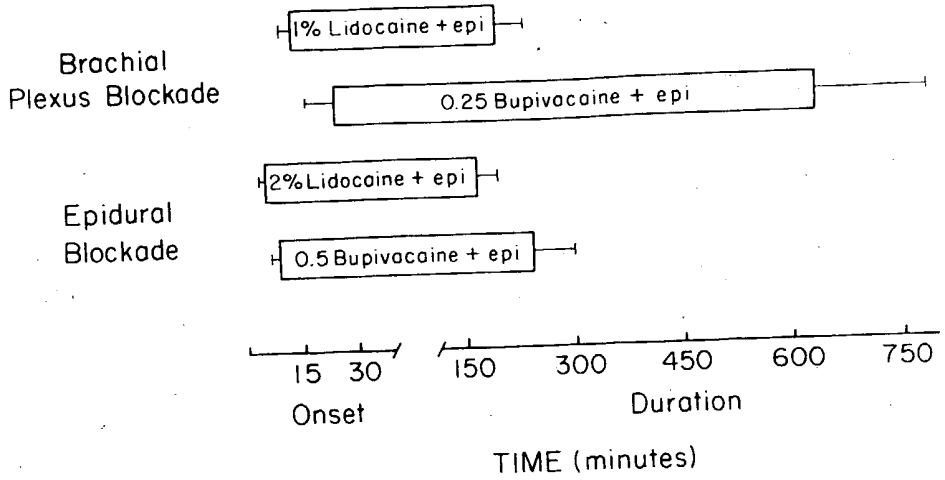


FIG. 4-5. Comparative onset and duration of anesthesia of lidocaine and bupivacaine following epidural and brachial plexus blockade.

Use of Additives with Local Anesthetic Solutions

Attempts have been made to modify local anesthetic solutions in a number of ways in order to improve the onset of action or prolong the duration of anesthesia. Carbonation of local anesthetic solutions has been attempted to reduce the onset of action of various local anesthetics (Fig. 4-6). It has been clearly shown in isolated nerve preparations that carbon dioxide will enhance the diffusion of local anesthetics through nerve sheaths and produce a more rapid onset of conduction block.[29,62] The mechanism is believed to be related to the diffusion of carbon dioxide through the nerve membrane resulting in a decrease in intracellular pH. The lower pH will increase the intracellular concentration of the cationic form of the local anesthetic, which represents the active form that binds to a receptor in the sodium channel. In addition, the local anesthetic cation does not readily diffuse through membranes such that the drug remains entrapped within the axoplasm, a situation referred to as ion trapping. The enhanced formation of the local anesthetic cation and the process of ion trapping are believed responsible for the more rapid onset and more profound degree of conduction block. A number of clinical studies have been carried out with carbonated solutions of lidocaine. Initial investigations in humans found that lidocaine carbonate solutions had a more rapid onset of brachial plexus and epidural blockade compared to lidocaine hydrochloride solutions.[18,20] More recent double-blind studies, however, have failed to demonstrate a significantly more rapid onset of action when lidocaine carbonate was compared with lidocaine hydrochloride for epidural blockade.[107] In theory an agent such as bupivacaine that has a relatively slow onset of action should benefit greatly from the use of a carbonated solution, and it has been reported that bupivacaine–carbon dioxide is associated with a more rapid onset of action in humans[47]; however, double-blind studies in which bupivacaine carbonate was compared with bupivacaine hydrochloride for brachial plexus or epidural blockade have failed to confirm these earlier reports of a significantly shorter onset of action of the carbonated solution.[25,100] Thus, at present, it is not certain whether carbonation of local anesthetic solutions imparts any advantage to the various local anesthetic agents in terms of onset of block when used under clinical conditions, although the depth of anesthesia may be improved.

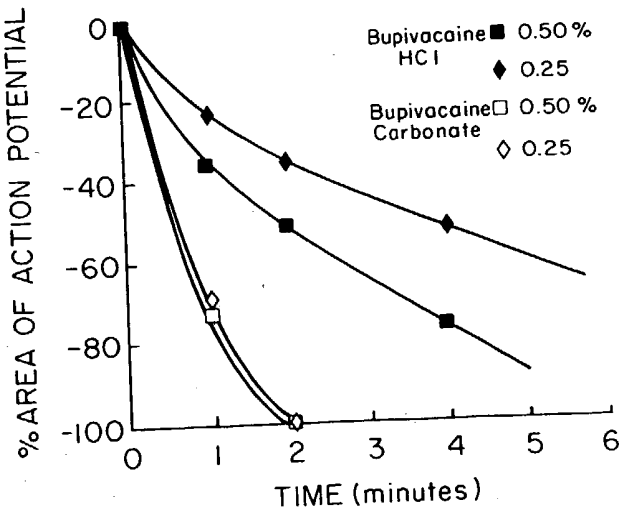


FIG. 4-6. Effect of CO_2 on the onset of conduction block in the isolated frog sciatic nerve.

The discrepancy between *in vitro* and *in vivo* studies suggests that the injected carbon dioxide is rapidly buffered *in vivo* such that the intracellular pH is not sufficiently altered and significantly increased levels of the cationic form of the local anesthetic are not achieved to produce a more rapid onset of anesthesia.

Attempts have been made to improve the onset of conduction blockade by adding sodium bicarbonate to local

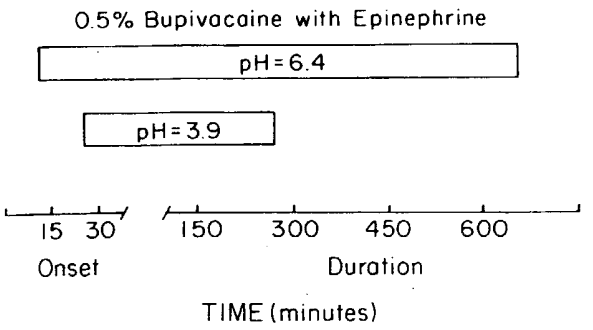


FIG. 4-7. Effect of pH on the onset and duration of brachial plexus blockade. (Data derived from Hilgier, M.: Alkalinization of bupivacaine for brachial plexus block. Reg. Anesth., *10*:59, 1985.)

anesthetic solutions immediately before injection.[59,74] Theoretically, sodium bicarbonate will increase the pH of the local anesthetic solution, which in turn will increase the amount of drug in the uncharged base form. Thus the rate of diffusion across the nerve sheath and nerve membrane should be enhanced, resulting in a more rapid onset of anesthesia. Several clinical studies have been performed in which the addition of sodium bicarbonate to solutions of bupivacaine did appear to produce a significant decrease in the latency of brachial plexus blockade.[59,74] Moreover, it has been reported that the duration of anesthesia was prolonged by increasing the pH of the local anesthetic solution (Fig. 4-7).[74]

Potassium has also been added to local anesthetic solutions in an attempt to improve the quality of anesthesia. Addition of 1% KCl to lidocaine was found to shorten the latency of spread and intensify the quality of sensory block in the epidural space.[22] In a subsequent study, the duration of digital and ulnar blocks with lidocaine was prolonged by the addition of KCl, but the onset of anesthesia was unaffected.[4]

Various attempts have been made to prolong the duration of anesthesia by incorporating dextran into local anesthetic solutions.[96,122] Discrepancies exist in studies of the effectiveness of dextran in prolonging the duration of regional anesthesia. In one controlled clinical study, prolonged durations of anesthesia were observed in some patients, but the mean duration of intercostal nerve blockade was not significantly altered when solutions of bupivacaine with and without dextran were compared.[14]

Rosenblatt and Fung have suggested that the difference in results obtained by various investigators may be related to the pH of the dextran solution used.[123] These authors have reported that dextran solutions with a pH of 8.0 significantly prolong the duration of bupivacaine-induced coccygeal nerve blocks in rats, whereas the duration of block is not altered when dextran with a pH of 4.5 to 5.5 is added to bupivacaine.[123] These results indicate that alkalinization of the anesthetic solution may be responsible for prolonged conduction blockade rather than the dextran itself.

Mixtures of Local Anesthetics

The use of mixtures of local anesthetics for regional anesthesia has become relatively popular in recent years. The basis for this practice is to compensate for the short duration of action of certain agents such as chloroprocaine or lidocaine and the long latency of other agents such as tetracaine and bupivacaine. The combination of lidocaine or mepivacaine and tetracaine was commonly used in some centers before the advent of bupivacaine and etidocaine as long-duration anesthetics. Because the slow onset of tetracaine for peripheral nerve blocks and epidural anesthesia was clinically unacceptable, the addition of lidocaine or mepivacaine provided a local anesthetic solution that afforded a relatively rapid onset of action and prolonged duration of anesthesia. Further, mixtures of chloroprocaine and bupivacaine have been used to produce a local anesthetic solution with a rapid onset and long duration of action. The low systemic toxicity of chloroprocaine afforded an additional advantage to such a mixture; however, the use of a chloroprocaine-bupivacaine mixture has produced contradictory results. Cunningham and Kaplan originally reported that a mixture of chloroprocaine and bupivacaine did result in a short latency and prolonged duration of brachial plexus blockade.[42] On the other hand, Cohen and Thurlow found that the duration of epidural anesthesia produced by a mixture of chloroprocaine and bupivacaine was significantly shorter than that obtained with solutions of bupivacaine alone.[35] This reduced duration has been attributed in part to a decrease in pH, since chloroprocaine solutions have a pH of about 3.0.[60] Reduction in pH will decrease the amount of bupivacaine available in the uncharged base form, which may reduce the number of molecules able to penetrate the nerve sheath. In addition, data from isolated nerve studies suggest that a metabolite of chloroprocaine may inhibit the binding of bupivacaine to membrane receptor sites.[38] In a randomized prospective study of mixtures of various concentrations of lidocaine and bupivacaine, no difference in onset of blockade was observed among the solutions tested. Duration of blockade with a 50:50 mixture of lidocaine/bupivacaine was only marginally greater than that for lidocaine alone.[132] At present there do not appear to be any clinically significant advantages to using mixtures of local anesthetic agents. Etidocaine and bupivacaine provide clinically acceptable onsets of action and prolonged durations of anesthesia. In addition, the use of catheter techniques for epidural anesthesia and for brachial plexus blockade makes it possible to administer repeated injections of rapidly acting agents such as chloroprocaine or lidocaine, which will provide an anesthetic duration of indefinite length.

TOXICITY OF LOCAL ANESTHETICS

Various types of toxic reactions have been reported in humans in association with the use of local anesthetic agents. The adverse reactions observed include systemic toxicity involving primarily the central nervous system (CNS) and the

cannulation, application prior to neural blockade, skin graft harvesting, arteriovenous shunt procedures, lumbar puncture, and as a method of anesthetizing gums prior to local anesthetic blocks for dentistry.[27,33,138]

The availability of EMLA patches[33] over the counter in some countries introduces the "patient control" concept to local anesthesia. Patients, or parents of children, appropriately instructed, can apply the patch prior to a painful procedure; this permits a sense of control, may reduce anxiety, and may increase patient satisfaction with the procedure. The "regional block" anesthesiologist can also apply EMLA, or instruct the patient to do so, prior to a neural blockade technique, thus preparing the area for a more comfortable start to the procedure.

Bupivacaine

Bupivacaine has probably had the greatest influence on the practice of regional anesthesia since the introduction of lidocaine. Bupivacaine was the first local anesthetic that combined the properties of an acceptable onset, long duration of action, profound conduction blockade, and significant separation of sensory anesthesia and motor blockade. This agent is used in concentrations of 0.125%, 0.25%, 0.5%, and 0.75% for various regional anesthetic procedures, including infiltration, peripheral nerve blocks, and epidural and spinal anesthesia. Bupivacaine has not been used for topical anesthesia. The average duration of surgical anesthesia of bupivacaine varies from about 3 to 10 hours. Its longest duration of action occurs when major peripheral nerve blocks such as brachial plexus blockade are performed. In these situations, average durations of effective surgical anesthesia of 10 to 12 hours have been reported. In some patients, durations of brachial plexus block of 24 hours or more have been observed with complete recovery of sensation. The vascular absorption of bupivacaine is influenced to a variable extent by epinephrine, but less so than for lidocaine.

The major advantage of bupivacaine appears to be in the area of obstetric analgesia for labor. In this situation, bupivacaine administered epidurally in concentrations varying from 0.125% to 0.5% provides satisfactory pain relief for 2 to 3 hours, which significantly decreases the need for repeated injections in the pregnant woman. More importantly, adequate analgesia is usually achieved without significant motor blockade such that the woman in labor is able to move her legs. This differential blockade of sensory and motor fibers is also the basis for the widespread use of bupivacaine for postoperative epidural analgesia and for certain chronic pain states (see Chapters 18, 26, 29).

Unfortunately the obstetric use of bupivacaine has been tempered somewhat in the mid 1980s because of reports of sudden cardiovascular collapse following the accidental rapid intravenous administration of this agent. The cardiotoxicity of bupivacaine, which has been discussed previously, has occurred primarily in the United States in obstetric patients. As a result, the 0.75% solution of bupivacaine is no longer recommended for obstetric anesthesia in the United States.

Bupivacaine had become relatively popular for intravenous regional anesthesia. The advantage of bupivacaine for intravenous (IV) regional anesthesia is related to the suggestion that there was an extended duration of anesthesia that occurred after tourniquet deflation. Several reports of sudden cardiovascular collapse after accidental early cuff deflation have resulted, however, in a recommendation in the United States that bupivacaine not be used for IV regional anesthesia (see Chapter 12).

In recent years, bupivacaine has been used extensively for spinal anesthesia. Isobaric and hyperbaric solutions of 0.5% to 0.75% bupivacaine have been investigated for various surgical procedures performed under subarachnoid blockade. Onset of spinal anesthesia with bupivacaine usually occurs within 5 minutes, whereas the duration of surgical anesthesia persists for 3 to 4 hours. Comparative studies of bupivacaine and tetracaine suggest little difference between the two agents in terms of onset, spread, and duration of spinal blockade. Several investigations have suggested that the frequency of satisfactory anesthesia may be greater with bupivacaine than with tetracaine. In addition, less hypotension is apparent after the intrathecal administration of bupivacaine, even in patients with an exaggerated spread of sensory anesthesia. The degree of motor blockade is greater when isobaric solutions of bupivacaine are used as opposed to hyperbaric formulations (see Chapter 7).

Ropivacaine

The concern about the potential of bupivacaine to produce cardiotoxicity after accidental intravenous injection, described earlier, has led to a search for an alternative long-acting local anesthetic drug. Ropivacaine has undergone considerable laboratory and clinical evaluation and has recently become approved for clinical use by the regulatory process in many parts of the world; it is not yet commercially available in any country. It belongs to the same chemical series as mepivacaine and bupivacaine, being intermediate in structure between the two agents (Chapter 3, Fig. 3-6). All the compounds in this series contain an asymmetric carbon atom which means that they may exist (and are usually presented) as a racemic mixture of two, optically active isomers.[99]

However, ropivacaine is unique in that it was marketed as an almost pure solution of the *S* isomer. This isomer was chosen because it is the longer acting of the two when used for nerve blockade in animals. Subsequent work has shown that the *S* isomer is also less cardiotoxic than the *R* isomer[147] so there is a double advantage (see also Chapter 3). Intravenous infusion studies in man have shown that ropivacaine can be administered in larger doses than bupivacaine before

arly features of both cardiovascular and CNS toxicity are pparent.[88,130] The implication is that the higher concentrations of ropivacaine (e.g., 0.75 or 1.0%) may be used with ess risk of severe toxicity than is the case with bupivacaine.[99]

Early clinical studies have suggested that ropivacaine has block profile very similar to bupivacaine (but with a marginally shorter duration) when used for major peripheral[72,73] and epidural[17,23,36,82] block. In addition, the epidural studies also suggest that the degree of motor block produced by ropivacaine is less than that produced by bupivacaine so it may be possible to produce a greater separation between sensory and motor block when the agent is used for pain relief in the postoperative period or during labor[99] (see also Chapter 8).

Ropivacaine has already undergone significant evaluation in these latter fields (although the work is not yet published), and it is likely to be the first agent to be marketed in most countries in a dilute formulation for constant infusion. Like other local anesthetics, ropivacaine has a biphasic effect on blood flow,[30] but the vasoconstrictor action is present at clinically used concentrations, the agent having been shown to reduce epidural blood flow.[43] Thus it is unlikely to be marketed in preparations containing epinephrine.[99]

Etidocaine

Etidocaine, which is chemically related to lidocaine, is one of the more recent local anesthetics introduced for clinical use. This agent is characterized by very rapid onset, prolonged duration of action, and profound sensory and motor blockade. Etidocaine may be used for infiltration, peripheral blockade, and epidural anesthesia. Although etidocaine and bupivacaine provide prolonged durations of anesthesia, significant differences exist with regard to the anesthetic profile of these two local anesthetics. Etidocaine has a significantly more rapid onset of action than bupivacaine. In addition, the concentrations of etidocaine required for adequate sensory anesthesia produce profound motor blockade. As a result, etidocaine is primarily useful as an anesthetic for surgical procedures in which muscle relaxation is required. For this agent is of limited use for obstetric epidural analgesia and for postoperative pain relief because it does not provide a differential blockade of sensory and motor fibers. It is possible to take advantage of the different pharmacologic profiles of etidocaine and bupivacaine in certain clinical situations. For example, it is possible to initiate epidural blockade with 1.5% etidocaine for lower limb orthopedic procedures, such as total hip replacements, and for abdominal surgical procedures. Under these conditions etidocaine will provide a rapid onset of action and a profound depth of anesthesia and muscle relaxation. Supplemental intraoperative and postoperative anesthesia is then provided by 0.5% bupivacaine, which produces excellent sensory anesthesia with minimal motor blockade. Effects of epinephrine on vascular absorption of etidocaine are summarized in Chapter 3.

Agents Currently Undergoing Evaluation

Articaine

Articaine is an agent that has been used in dental practice in some European countries for nearly 20 years. It belongs to the anilide group of local anesthetics, but differs from drugs such as lidocaine in that it has a thiophene ring instead of a benzene ring in its structure.[149] It has been claimed that this agent has a faster onset and better spreading properties than lidocaine when used in dental blocks and this has resulted in its reevaluation for wider use. However, comparison with prilocaine in dental blocks has not demonstrated any difference[68] and comparison with lidocaine in epidural use also failed to show any significant differences.[16] Thus it seems unlikely that this agent will become much more widely available.

Butamben

Butyl aminobenzoate (BAB) is an amino ester local anesthetic patented in 1923 and originally used as a topical preparation, Butesin Picrate (Abbott Laboratories, North Chicago, IL). BAB is an ester of *para*-aminobenzoic acid and butyl alcohol, with a molecular weight of 193.24. An extraordinarily low pKa of 2.3 results in minimal ionization to the hydrophilic cation, and thus BAB is at the extreme low end of local anesthetic water solubility.[65]

BAB also has poor dural permeability, and these properties, together with its rapid hydrolysis, were previously thought to make it unattractive for epidural use. However, in the late 1980s, Shulman in the United States and Korsten in the Netherlands contemporaneously formulated suspension preparations of BAB, which produced long-lasting sensory blockade when given epidurally to cancer patients.[84,133] Subsequently Abbott Laboratories overcame substantial theoretical and technical difficulties to prepare a reproducible aqueous *suspension* of 5% butamben composed as follows: Each milliliter of BAB suspension contains 50 mg BAB; 0.25 mg polysorbate-80 (Tween-80) and 25 mg polyethylene glycol (PEG-3350) as suspending agents; and 9 mg sodium chloride for tonicity adjustment. The suspension has a pH of approximately 6.0 and a mean particle size of about 40 μm. Since 1 g of BAB dissolves in about 7 liters of water, very little of the BAB in the *suspension* is present in aqueous *solution* and thus the majority of BAB is present in a solid form which acts as a depot for very slow dissolution. In this respect the BAB suspension is like "slow-release" morphine preparations, where it is not the drug *per se* that is long-acting but the slow and *continuous* release of the drug. This explains the extraordinarily long duration (weeks to months) of pain relief associated with epidural butamben *suspension* administration in patients with cancer pain[84,133];

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On the other hand, many antihistaminics have some local anesthetic activity. Thus, tripelennamine has been used for topical anesthesia of the pharynx and larynx. Local anesthetic activity has been demonstrated for ephedrine, meperidine, atropine, and many other similar agents.

Antithrombotic Action

Many local anesthetics have an antithrombotic effect. The *-amide* drugs, in particular, demonstrate this action. A primary effect on hemostasis occurs by inhibition of platelet aggregation.[21] Lidocaine has a high potency for this action, while bupivacaine demonstrates it to a lesser extent.[22] The effect appears to increase with time. In an experimental study, higher concentrations of lidocaine were needed than are clinically used or achieved after epidural injections.[23] However, in combination with other factors, the antithrombotic action may have clinical relevance. A lower incidence of thromboembolism occurs after epidural anesthesia for many surgical procedures partially through improved rheological conditions, but a direct antithrombotic effect of absorbed lidocaine may be contributory.[24] In addition, studies by Stewart[23] and Luostarinen[22] showed that local anesthetics exert a blocking action on leukocyte locomotion and prevent these cells from adhering to, and invading, venous walls, thereby preserving the endothelial structure.

Antimicrobial Effect

An antimicrobial effect of local anesthetics was first suggested by Jonnesco in 1909.[25] Since then, many local anesthetics have been shown to possess this activity.[26,27]

Tetracaine has been known to inhibit cultures of bacteria from sputum samples taken during bronchoscopy under such topical anesthesia.[26] Studies by Kleinfeld[26] demonstrated that 2% tetracaine instilled into the trachea of patients with active tuberculosis inhibited the culture of the tubercle bacilli in sputum samples taken for as long as 5 days after the topical anesthesia.

The mechanism of action may be related to the chemical structure of tetracaine, which is a paraamino benzoic acid. In this regard, it resembles paraamino salicylic acid, which is used to treat tuberculosis. In addition, tetracaine has also been shown to cause cell lysis of *Pseudomonas aeruginosa*. The effect of tetracaine is direct and topical in nature and caused by a systemic mechanism. It is a direct destructive effect on the bacteria.

In vitro testing of lidocaine and procaine against gram-negative and gram-positive bacteria, tubercle bacilli, and fungi, showed inhibition of microbial growth.[28] The inhibition of bacterial growth by 2% lidocaine, however, is only about one-half the potency exhibited by 2% tetracaine. Gram-negative bacteria are particularly sensitive, as is *Escherichia coli*, to these two drugs.

Bupivacine, at a concentration of 2.5 to 5.0 mg/mL (standard epidural concentrations), inhibits most gram-negative microorganisms, with the clear exception of *P. aeruginosa*.[29]

In terms of mechanism, lidocaine has been shown to change the permeability of the cell wall and to inhibit the intracellular incorporation of precursors of DNA, RNA, and protein formation. This disruptive effect provides insight into antimicrobial action.

Clinical Relevance

Topical tetracaine in ophthalmologic and endoscopic practice may provide protection of the operator from patient infections. It also may diminish viability and spread of pathogenic organisms in the patients.

With regard to epidural injection of local anesthetics, either by single dose or by catheter technique, reports of epidural abscess and other infections are rare. This may be attributed to the antimicrobial effect of bupivacaine and lidocaine as the epidural anesthetic agents.[29]

GENERAL CHEMISTRY OF LOCAL ANESTHETICS[30,31]

Qualitative and quantitative differences chemically and variations in tolerance, potency, and toxicity provide a wide spectrum of local anesthetics available to serve specific needs (Table 42–4).

Local anesthetic drugs may be divided chemically into three general groups (Table 42–4). These are the esters, the amides, and the alcohols and miscellaneous synthetics. The first group contains the majority of drugs in common use. These are complex esters. Esters are formed when an alcohol reacts with an acid. Nitrogen in the form of a tertiary amine, either on the acid or the alcohol part of the molecule, or on both, confers basic properties to these drugs. The nitrogen may exist as the unchanged tertiary amine (free base) or as the positively charged ammonium cation. Which form is present depends upon the pK of the specific agent and the pH of the solution in which it is dissolved. Most pK values are between 8 and 9. Thus, at a tissue pH of 7.4, only 5 to 20% exists as the free base.

The second group, which is relatively unimportant, consists of phenolic and alcoholic compounds used for skin and surface anesthesia. The third group consists mainly of compounds containing nitrogen.

With the exception of cocaine, local anesthetic drugs are all synthetic compounds with many of the general properties of alkaloids. They contain nitrogen and are themselves basic in reaction and bitter

TABLE 42–4. CHEMICAL CLASSIFICATION OF LOCAL ANESTHETIC DRUGS

ESTERS
1. Benzoic acid esters: cocaine, piperocaine, hexylcaine
2. Amino-benzoic acid esters:
(*a*) Soluble type: procaine, chlorprocaine; tetracaine; butyn
(*b*) Limited solubility type: benzocaine and butesin
3. Para-ethoxy-benzoic acid: intracaine
4. Carbamic acid ester; diothane
5. Complex synthetics
AMIDES
1. Straight chain acid derivatives of Xylidide
Acetic acid: xylocaine (Lidocaine)
Propionic acid: propitocaine (Citanest)
2. Pipecolic acid derivatives of Xylidide
mepivacaine (Carbocaine)
bupivacaine (Marcaine)
3. Oxycinchoninic acid
dibucaine (Nupercaine)
ALCOHOLS
1. Etyhl alcohol
2. Aromatic alcohols: benzyl; saligenin
MISCELLANEOUS
1. Complex synthetics: holocaine
2. Quinoline derivatives: eucupin
3. Ammonium Compounds (TEA)

to taste. They form salts that are solids with inorganic acids, such as hydrochloric and sulfuric, and the powders are oily to touch. The clinically useful local anesthetics are nitrogen containing and, with few exceptions, are amines. These salts are acid in reaction, and when treated with alkalies, the free base is precipitated. The free base generally is insoluble in water. The free bases are readily soluble in lipoids and lipoid solvents. The bases redissolve in acid to again form the salt in the same manner in which ammonia combines with acid ($NH_3 + HCl = NH_4 + Cl$). These drugs give the usual color reactions and precipitation tests for the alkaloidal reagents. Local anesthetics are readily absorbed and they lower surface and interfacial tensions.

ESTER COMPOUNDS[31]

Esters represent compounds formed from a combination of an aromatic acid with an alcohol.

The most common ester group of local anesthetics is that consisting of derivatives of *para*-amino benzoic acid $H_2N-C_6H_4-COOH$. Procaine, which is the amino-benzoic acid esterified with di-ethyl ethanolamine, is the most prominent of this series. Such drugs as tetracaine, chlorprocaine, and butyn are esters of amino-benzoic acid and various amino alcohols.

In this group are some agents of limited solubility, such as benzocaine, which is used in dusting powders and ointments (3 to 5%), and butacaine sulfate used topically as an ENT preparation 2%.

A second important chemical division of esters is derived from pure benzoic acid. Cocaine is the benzoic acid ester of methyl ecognine. Several compounds have been prepared which are modifications of the cocaine type of structure and have less toxicity. The eucaines and tropocaines, which are little used today, are typical. Synthetic compounds in this group are piperocaine and hexylcaine.

A third group of compounds derived from para-ethoxy benzoic acid esterified with amino alcohols, has been prepared. The amino (NH_2) group of the benzoic acid is replaced with the ethoxy radicle $-O-C_2H_5$. The homologue to procaine in this series has been marketed as "Intracaine," which is a satisfactory drug for infiltration anesthesia but not currently used.

AMIDE DERIVATIVES[32]

These local anesthetic agents are quite different chemically and pharmacologically from the ester compounds. Amides are commonly prepared by the reaction of an organic acid with ammonia or an amine. They are benzoic acid derivatives and contain either the chemical group ($-NH-CO-CH_2$) or ($-CO-NH-CH_2$). They are distinctly non-esters.

In contrast to the ester compounds that are detoxified in the bloodstream, the amides are not inactivated by blood cholinesterases; they are primarily detoxified in the liver by hydrolysis.

Sensitivity reactions which frequently occur with the ester compounds are not usually exhibited by the amide compounds. There is no cross tolerance or cross sensitization. The patient who is sensitive to a member of the ester drugs does not exhibit sensitivity to amide drugs. Differences in sensitivity also are to be noted between dibucaine and lidocaine. In the structure of these two drugs the orientation of the identifying chemical group ($-NH-CO-$) is in opposite directions from the benzene ring. Thus, there is little or no cross-sensitivity or tolerance between dibucaine and the other amides.

ALCOHOL GROUP

Certain aromatic alcohols are valuable in producing surface anesthesia. They contain no nitrogen, are neutral or slightly acid in reaction, and are somewhat soluble in water. The most important member is benzyl alcohol (liquid). It is relatively nontoxic, but the surface anesthesia resulting from its use is spotty. It is used chiefly in the form of a lotion or ointment in dermatology.

MISCELLANEOUS NON-ESTERS

Several of the local agents in the non-ester group are aniline derivatives. Eucupin, similar in structure to quinine, has a longer side chain and is prepared from quinine. Holocaine is prepared from para-ethoxy aniline (phenetidin), which forms the basis of phenacetine and other antipyretics.

MIXTURES OF LOCAL AGENTS[31,32]

A mixture of an agent with a short duration and rapid onset of action with one that has a slow onset of action but a long duration has been proposed. It is particularly considered that an amide and an ester should be combined. Thus, lidocaine or mepivacaine could be mixed with tetracaine; chlorprocaine or lidocaine (short-acting agents) could be mixed with bupivacaine or tetracaine (long-acting agents). An early combination recommended consisted of lidocaine or mepivacaine (amides) with tetracaine (an ester) and used clinically. A mixture of chlorprocaine (an ester) with bupivacaine (an amide) was reported to provide a short latency and long duration of brachial plexus block.[33] Such a mixture used for extradural anesthesia, however, was not found to provide a long duration of action.[34]

Commonly recommended is chlorprocaine (an ester) with bupivacaine (an amide). Studies by Galindo[35] showed that the effects of one predominate over the other, depending on pH. A commercial preparation of chlorprocaine 1% with bupivacaine 0.25% at pH 3.8 produced a block characteristic of chlorprocaine; at a pH of 5.6, the block was characteristic of bupivacaine. It should be noted that the available base of the bupivacaine at pH 3.8 was one-hundredth that available at pH 5.6.[35]

Currently, mixtures do not appear to provide significant advantages. The use of continuous technique of administration of the short-acting agents, such as lidocaine or chlorprocaine, provide clinical flexibility. (See also "Topical Anesthesia" section.)

COMPARATIVE PHARMACOLOGIC PROPERTIES[36,37] (Table 42–5)

PHARMACODYNAMICS

Onset of Action

Onset of action is related to the ionization constant (pK_a) of each agent.[38] Since the diffusion of an agent across the nerve membrane[39] is related to the uncharged form of the local agent, the base form which is the effective blocking form,[39a] the number of molecules of this form determines the speed of onset. The percentage of a local anesthetic agent is related to the pK_a of the agent and to the pH of the medium into which it is placed. *The physiochemical principle states that the amount present in the base form (nonionized) is inversely proportional to the pK_a of the agent at a given pH of the medium* (Table 42–6).[39a] Mepivacaine, etidocaine, lidocaine, and prilocaine all have pK_a values of about 7.7 and 7.9 and, when injected into tissue, these drugs will ionize so that approximately 65% will be in the ionized form and 35% in the base form. Hence, the uptake by the nerve membrane is rapid, and the onset of action is fast.

In contrast, tetracaine has a pK_a of 8.6, and the other conventional amino esters with a pK_a of 8.7 (chlorprocaine) and 8.9 (procaine) are ionized extensively in tissues at pH 7.4 up to 95% or more, and only 2 to 5% is in the nonionized form. The uptake at nerve membranes is impeded, and the onset of block is slow. Bupivacaine, with a pK_a of 8.1, is intermediate, with only 15% in the base form, and the rest is ionized as the cation.

The clinical correlation is that agents with the low pK_a and the high percentage in base form (mepivacaine and lidocaine) penetrate the neural membrane relatively quickly, and the onset of block is rapid. Tetracaine and procaine have a slow onset, while bupivacaine has an intermediate speed of onset[39] (Fig. 42–3 and Table 42–7).

INFLUENCE OF SITE OF ADMINISTRATION ON ONSET. The site of administration of a local anesthetic modifies the pharmacodynamic profile. The most rapid onset of anesthesia occurs following subcutaneous or subarachnoid administration. The slowest onset times are observed in the performance of brachial plexus blocks.[40] The rapidity of onset of spinal anesthesia is readily understood because of the deposition of the local anesthetic in the vicinity of the nerve roots at the spinal cord level and also to the lack of sheaths about the nerve roots.

In performance of brachial plexus block, the anesthetic solution is deposited away from the nerve roots, and a longer time for diffusion to the nerves is required.

Effect of Dosage on Dynamics

The amount of drug administered affects the onset, duration, and quality of anesthesia. Increasing the dose within the clinical range enhances the quality of anesthesia, as seen by the *adequacy* and frequency of satisfactory anesthesia. This is determined by two factors: (1) by the speed of onset of the anesthesia, and (2) by the increase in duration of anesthesia.

A dose-response relationship can be demonstrated in extradural anesthesia with etidocaine.[36] As the dose increases, there is an improvement in the anesthetic response: onset time is shortened, duration is increased, and the frequency of satisfactory anesthesia approaches 100% (Fig. 42–4).

of 1:200 is used (5 mg/mL) for spinal anesthesia; a hypobaric solution of 1:1500 dilution in 0.5% saline known as Jones' solution is widely used. It has a specific gravity of 1.0025 at 25°C.

The drug is slowly detoxified. Its spinal anesthetic effect is prolonged up to 4 hours.

Nupercaine in 0.1% solution is used for topical anesthesia and has proved effective.

Ointments containing 1% Nupercaine base are available for dermatologic practice.

LIDOCAINE (XYLOCAINE)

Source

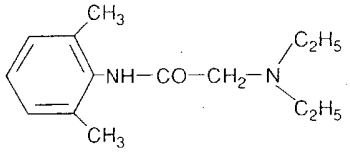
Lidocaine is a synthetic compound and was first prepared in 1943 by Löfgren.[4]

Chemical Name

Lidocaine's chemical name is diethylamino-2,6-acet-oxylidide. It is essentially an amide or anilid resulting from the reaction of diethylaminoacetic acid and an ammonia-containing substance, xylene.

The molecular weight of the base is 234, and of the hydrochloride salt is 270.

CHEMICAL STRUCTURE. Its chemical structure is



Physiochemical Properties

SOLUBILITY. Lidocaine is freely soluble in water; the pH of 1% solution in 0.9% saline is 6.5 to 7.0.

STABILITY. Lidocaine is very stable; it may be boiled for eight hours in 30% hydrochloric acid without decomposition.

STERILIZATION. Lidocaine can be sterilized by boiling or autoclaving; crystals may be autoclaved for 6 hours or subjected to multiple autoclaving without loss of potency.

Toxicology

CYTOTOXICITY. Lidocaine is not irritating to tissues, even at a concentration of 88%.

SYSTEMIC TOXICITY. Lidocaine is one-fifth as toxic as cocaine and 1.5 times more than procaine.

POTENCY. Lidocaine's potency is three times that of procaine.

ANESTHETIC INDEX. Lidocaine has an anesthetic index of 2.0 to 3.0 for infiltration with 0.5%, and 1.0 for block anesthesia with 2%.

Disposition of the Drug

This drug requires approximately two hours for disappearance from cutaneous and subcutaneous sites of infiltration. When epinephrine is used in conjuction with the solution, the rate of disappearance is prolonged to about four hours. The anesthetic has a high affinity for fat tissues. After injection, concentrations of the drug are found in various organs.[123] The highest concentration is found in the kidney; other appreciable levels are found in the lungs, spleen, heart, and brain; rather low levels are found in the liver and blood.

BIOTRANSFORMATION. The disposition of lidocaine is mainly by biotransformation.[59] The metabolism is accomplished in the liver by microsomal mixed function oxidases. The initial reaction in this process is dealkylation of the lidocaine in the following sequence: (1) to monoethylglycine-xylidide (MEGX); (2) the second product of the major pathway of metabolism is the formation of 2,6-xylidine; and (3) this particular product is metabolized further by hydroxylation of the ring structure. The major lidocaine urinary metabolite in humans is a conjugate of the resulting hydroxylated product[124] (See Fig. 42–8).

The major lidocaine urinary metabolite is represented as a conjugate of 4-hydroxy-2,6-xylidine. Approximately 73% of a given dose is eliminated in the urine in this form.

A minor pathway of biotransformation is that of MEGX to glycine-xylidide (GX). An additional urinary fraction is the conjugate of GX. Approximately 3% of lidocaine is excreted in the free form unchanged.

It is recognized that two of the transformation products, i.e., MEGX and GX, both of which are dealkylated products, continue to have activity.[125] For example, a MEGX metabolite has anti-arrhythmic properties equivalent to that of the parent drug lidocaine. It may be that toxic cardiac effects are related to MEGX. It also possesses anesthetic local activity. One further factor is the contribution to the convulsive effect of xylocaine itself, and MEGX and intact lidocaine are additive.[125] This is pronounced in animal work. GX appears, on the other hand, to have central effects. It induces headache and alters mental performance. It also potentiates the convulsive activity of MEGX and has CNS depressant activity.

Evidence indicates that fetal metabolism of lidocaine occurs with the formation of the same metabolites MEGX and GX, as well as the 2,6-xylidine and the hydroxy form.[126]

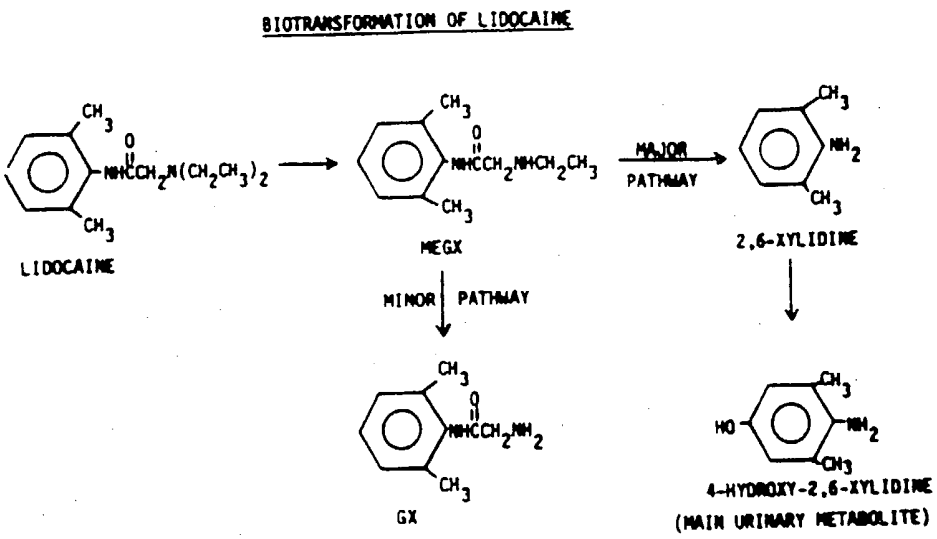


FIG. 42–8. Chemical structures for lidocaine and its metabolites in humans. From Drayer, D.E., et al.: Clin. Pharmacol. Ther., *34*: 14–22, 1983. With permission.

Anesthetic Properties

Surface anesthesia is produced by a solution of 5% concentration, but it is not satisfactory. It may be used in urology.

LOCAL ANESTHESIA. Penetrability is excellent, and the rate of onset is about twice as fast as that of procaine; duration of anesthesia with a 1% solution is about 1½ to 2 times longer than that of procaine.

The recommended dose range is 200 to 400 mg. The total dose should not exceed 4.5 mg/kg. The following concentrations of solutions are used for the indicated procedure:

Infiltration	0.5%
Small nerve block	1.0%
Large nerve block	1.5%
Epidural block	1.5–2.0%

Special Properties and Actions

CARDIAC ACTION. Lidocaine exerts an antiarrhythmic effect on ventricular arrhythmias.

Ordinary doses of lidocaine used for infiltration purposes may provide plasma levels that alter electrophysiologic properties of the heart.[127] The injection of 10 to 20 mL of 1.0% lidocaine (100 to 200 mg) can give peak plasma concentrations of 1.5 to 2.5 mg/L. This is an effective antiarrhythmic level, i.e., it is above 1.2 mg/L.[128] In diagnostic and electrophysiologic studies, this is important and may alter results. Doses of lidocaine should not, therefore, exceed 2.5 mg/kg of body weight. A good correlation between injected dose and plasma concentration has been shown by Nattel. Plasma levels can be predicted by multiplying the initial dose administered in mg/kg of body weight by 0.3 to give the peak level attained in mg/L.[129]

VENTILATORY RESPONSE TO CARBON DIOXIDE.[130a] Plasma levels of 3 to 4 μg/mL increase the sensitivity of medullary respiratory centers to carbon dioxide, and the slope of the CO_2 response curve is shifted to the left. On the other hand, plasma levels of 8 to 10 μg/mL, approximately subconvulsive levels, produce ventilatory depression and flattening of the CO_2 response curve.

EFFECTS ON SKELETAL MUSCLE. Lidocaine causes the extrusion of calcium from the sarcoplasmic reticulum.

EFFECT ON WOUND HEALING. Studies of possible interference with body defenses and wound asepsis have been conducted. Concentrations of lidocaine commonly injected into tissues significantly inhibit phagocytosis and the metabolism of human leukocytes *in vitro*. This may be an attribute of all local anesthetic agents.[130]

MEPIVACAINE

Source

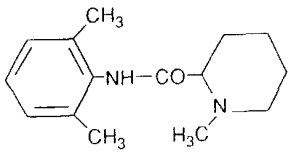
Mepivacaine is a synthetic compound first prepared by Dhunér,[131] and used clinically by Ekenstam in 1956.[132] It is known as Carbocaine.

Chemistry

Mepivacaine is a white, crystalline, odorless powder with a salty, bitter taste. The molecular weight is 282 and the melting point is 261°C. Carbocaine has an asymmetric carbon atom rendering it optically active. Both optical forms possess anesthetic potency, and the drug is available as a racemic mixture.

CHEMICAL NAME. Mepivacaine is 2,6 di-methyl anilide of d,l-N-methyl pipecolic acid. It is an amide resulting from the reaction of an amine (anilide) and an acid (pipecolic acid).

CHEMICAL STRUCTURE. Its chemical structure is



Physiochemical Properties

SOLUBILITY. The hydrochloric and other salts are freely soluble in water; the pH of a 1% solution in 0.9% sodium chloride is 4.8. The base is poorly soluble.

STABILITY. Both crystals and solution are thermostable. Mepivacaine is resistant to both alkaline and acid hydrolysis. Mepivacaine has a high chemical stability.

STERILIZATION. Mepivacaine may be autoclaved or boiled.

Toxicology

CYTOTOXICITY. Mepivacaine is less irritating than physiologic saline. It is significantly less cytotoxic than procaine and less than Xylocaine. Some changes are to be noted in skin after intracutaneous injection, and these include varying degrees of inflammation progressing to necrosis of cutaneous muscle. Some fibroblastic proliferation and formation of new capillaries occur.[133,134]

SYSTEMIC TOXICITY. Mepivacaine is three-fourths as toxic as procaine.

POTENCY. It is approximately two to four times more potent than procaine.

ANESTHETIC INDEX. Mepivacaine's anesthetic index is 3.0 to 4.0.

Disposition

The drug is absorbed into the bloodstream. In adults, three types of metabolic transformation occur. N-demethylation produces pipecolic acid, which is conjugated and excreted almost entirely (99%) as glucuronide. The ring structure undergoes two types of aromatic hydroxylation. Excretion of intact mepivacaine occurs to the extent of 5% to 10%, depending on urinary pH. In neonates, little metabolic degradation occurs, and 90% of the drug is excreted within 24 hours.[135]

Anesthetic Properties[136]

Mepivacaine is considerably more potent than procaine and somewhat more so than lidocaine. It is also less toxic both on tissues and systemically. Thus, the drug has a high anesthetic index and a wide margin of safety. It is effective in concentrations of 0.5% to 2.0%. The recommended concentrations for various types of regional procedures is as follows:

Infiltration anesthesia	0.5–1.0%
Block of small nerves	1.0%
Block of large nerves	1.5%
Epidural and caudal	1.5–2.0%
Spinal (experimental only)	2.0%

Dosage is determined by the type of block and the volume of solution needed to achieve the block. Arbitrary limits are as follows:

0 % concentration	125 mL (625 mg)
1.0% concentration	75 mL (750 mg)
1.5% concentration	50 mL (750 mg)
2.0% concentration	25 mL (750 mg)

Carbocaine can be used for most purposes without epinephrine. The addition of this vasoconstrictor provides insignificant advantage in terms of duration.

Carbocaine possess excellent penetrability, and the onset of action is quite rapid: Sensory anesthesia is established in 3 to 5 minutes after nerve blocks and in 8 to 10 minutes after caudal block.

The duration of action is from 2 to 2½ hours, and surgery can be performed in this period. Loss of cutaneous sense may continue for 3 hours.

Side Effects[136]

Serious systemic reactions are rarely encountered. Mild tachycardia and mild hypotension are seen. An occasional case of elevated blood pressure is also seen. This may indicate central stimulation. Twitching of the face muscles has been noted.

BUPIVACAINE

Source

Bupivacaine, a synthetic drug, was prepared by A. F. Ekenstam in 1957 and is marketed as Marcaine.[137]

Chemistry

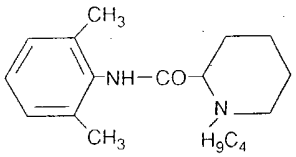
The molecular weight of the chloride salt is 325 and that of the baseform is 288. It has a melting point of 258°C. Solutions containing epinephrine have a pH of about 3.5.

CHEMICAL NAME. Bupivacaine is an anilide compound similar in chemical structure to mepivacaine.

The chemical name is 1-n-butyl-DL-piperidine-2-carboxylic acid-2, 6 dimethylanilide hydrochloride, which differs from mepivacaine in that a butyl group is substituted for a methyl group on the piperidine nitrogen.

Bupivacaine is thus a homologue of mepivacaine, with a molecular formula of $C_{18} \cdot N_2O \cdot H_{28} \cdot HCl$.

CHEMICAL STRUCTURE. Its chemical structure is



Physiochemical Properties[137,138]

SOLUBILITY. The base is sparingly soluble, but the hydrochloride is readily soluble in water.

Stability and Sterilization

Bupivacaine is highly stable and can withstand repeated autoclaving.

Anesthetic Properties[139,140]

POTENCY. Bupivacaine is approximately three to four times more potent than lidocaine or mepivacaine and eight times more than procaine. The duration of action for local anesthesia is two to three times longer than that of mepivacaine or lidocaine and 20 to 25% longer than that of tetracaine.

ANESTHETIC INDEX. Bupivacaine's anesthetic index is the same as mepivacaine's—3.0 to 4.0.

Bupivacaine is a reliable drug for infiltration and nerve block anesthesia but is unpredictable for spinal anesthesia. It appears to have a slow nerve-penetrating power. Excellent sensory anesthesia is produced. Although it has the same anesthetic index (potency/toxicity ratio) as mepivacaine, it has an excellent and more prolonged duration of sensory anesthesia, which is probably its most outstanding characteristic. Muscle relaxation with 0.5% bupivacaine is not profound, but fair motoneurone block is produced with 0.75% concentration.

Dosage

The recommended concentrations for various types of procedures is as follows:[140–143]

INFILTRATION. A concentration of 0.25% is used in healthy adults in volume-doses up to 70 and 90 mL with epinephrine. An 0.1% solution produces satisfactory anesthesia in debilitated patients and in children.[138]

NERVE BLOCK. The 0.5% solution usually is used up to a 35-mL volume which may be increased to 45 mL if epinephrine is added. This concentration is necessary to block large nerves and to produce complete motor block. A 0.25% solution is satisfactory for small peripheral nerves.[142,143]

CAUDAL. For obstetric analgesia and perineal surgery, the 0.25% solution is effective. A volume up to 30 mL may be used by the caudal technique. For surgery of the lower extremities, the 0.5% solution must be used and should be used if good motor block is desired.[144]

EPIDURAL BLOCK. For obstetric analgesia and perineal surgery, 20 mL of a 0.25% solution is effective. For lower extremity surgery, up to 20 mL of the 0.5% solution is satisfactory. For abdominal surgery, good conditions are achieved only by the use of 0.75% solution up to a volume of 20 mL.[145]

SUBARACHNOID BLOCK. Concentrations of 0.5–0.75% of bupivacaine are effective. A commercially available solution for subarachnoid block is a 0.75% bupivacaine plus 8.25% dextrose solution. This solution comes in a 2.0-mL ampule. Each milliliter contains 7.5 mg of bupivacaine and 82.5 mg of dextrose. It is adjusted to a pH ranging between, 4.0 to 6.5 by NaOH/HCl buffering. The specific gravity is 1.035 at approximately room temperature of 25°C. At body temperature (37°C), the specific gravity is 1.030. A 0.5% bupivacaine–5% dextrose solution may be prepared by adding 1.0 mL of saline to the 2.0 mL of the ampule volume. This solution is also available with epinephrine 1:200,000 premixed.

Plain bupivacaine hydrochloride is also available as a 0.75% solution in physiologic saline. This can be diluted by adding 1.0 mL of saline or cerebrospinal fluid to the 2 mL volume of the ampule, to make a 0.5% isobaric solution. The specific gravity is approximately 1.0066 37°C/37°C.[147]

Plain bupivacaine hydrochloride 0.75% in distilled water has a specific gravity of 1.0040 and is essentially hypobaric.[56a]

If muscle relaxation is desired in cases of nerve blocks and peridurals, an 0.75% solution is used.

The maximum recommended dose is 200 mg. If epinephrine is used, one should not exceed 250 mg. These doses may be repeated in 3 to 4 hours, but 400 mg is the maximum in 24 hours.[140,142]

Cumulative toxicity is reported as in the case of other amide local anesthetics.[139,140] However, the long duration of action makes it unnecessary for repeated frequent doses. The absence of muscle relaxation is rather advantageous for the initial pain relief (first stage) of obstetric patients. Initially, a 0.25% solution can be used, and when perineal relaxation is needed for the second stage, a higher concentration can be used.

Bupivacaine can be used with or without epineph-

rine. The addition of a vasoconstrictor provides a very slight increase in the duration of action. However, the peak blood level is significantly reduced, thereby minimizing the systemic toxicity.[140]

The Pharmaco Dynamics[139,140–143,148]

The onset of action of bupivacaine is between 5 and 7 minutes, and maximum anesthesia is obtained between 15 and 25 minutes. The duration of anesthesia varies according to the type of block; the average duration for peridural block is about 3.5 to 5 hours. For nerve blocks, it is about 5 to 6 hours.

SPINAL BLOCK. In spinal anesthesia, 0.75% bupivacaine is equivalent to 1% tetracaine. The onset of action is about 3 to 4 minutes, and complete anesthesia occurs in 5 minutes and lasts for 3.5 to 4 hours. The motor blockade is definitely inferior to tetracaine.[144]

A duration shorter than expected and less than mepivacaine, coupled with unreliability of action in spinal anesthesia, has been observed with volumes less than 8.0 ml. These features have curtailed its use by this technique.

Toxicology[139,148]

Bupivacaine, although chemically closely related to mepivacaine, is more like tetracaine in local anesthetic and toxicologic properties.

SYSTEMIC TOXICITY. The acute toxicity (LD_{50}) of bupivacaine is about the same as that of tetracaine, and approximately three to four times higher than that of mepivacaine. Maximum plasma concentrations rarely approach toxic levels. The toxic plasma concentration is set at 4 to 5 μg/mL.

CYTOTOXICITY. Bupivacaine and tetracaine have the same tissue toxicity. Nonspecific local irritant effects on nerve tissue have been noted in both animals and human subjects: no evidence of permanent damage has been found in clinical dosages. There is no alteration in the blood picture or methemoglobin formation because of this drug.

Pharmacokinetics

Bupivacaine can be detected in the blood within 5 minutes of infiltration or following either epidural or intercostal nerve blocks.[149] Plasma levels are related to the total dose administered. After a single-dose epidural or intercostal block, plasma bupivacaine concentrations within 1 to 2 hours of the onset of the anesthesia reach levels between 1 to 2 μg/mL.[149] Peak levels of 0.14 to 1.18 μg/mL were found within 5 minutes to 2 hours after the administration of the anesthesia, and they gradually declined to 0.1 to 0.34 μg/mL by 4 hours. The actual peak level depended upon the nature of the nerve block.[150] During continuous epidural analgesia, bupivacaine levels ranged between 1.0 to 3.0 μg/mL.[149]

Following intravenous infusion over a 3-hour period of bupivacaine, at a rate of 2.0 mg/min, significant and progressive increases in the bupivacaine, at a rate of 2.0 mg/min, significant and progressive increases in the bupivacaine plasma concentrations are observed steadily to 1.8 μg/mL. This is a concentration similar to that observed during regional anesthesia with bupivacaine.[151]

From the above studies on intravenous injection, it is evident that the alpha half-life in plasma of bupivacaine, after attaining levels of 1.0 to 2.0 μg/mL, is approximately 2.5 hours. The beta half-life is about 4 to 5 hours.[152]

Plasma Binding[140,153]

In plasma, the drug binds avidly with protein to the extent of 70% to 90%. The rank order of protein binding for this and its homologues is bupivacaine → mepivacaine → lidocaine. Conversely, the unbound active fraction is one-seventh that of lidocaine and one-fifth that of mepivacaine.

Metabolism–Elimination[153]

Because bupivacaine is an amide, the liver is the primary site of metabolism. When continuously administered intravenously to analgesic levels, bupivacaine is cleared from the plasma at the rate it is administered, and most of the drug is metabolized partly by N-dealkylation.[152] It crosses the placental barrier as any other local anesthetic by passive diffusion, but the lowest level of placental diffusion is reported for this drug (umbilical vein/maternal ratio is 0.31 to 0.44).[154] The high protein-binding capacity of this agent is probably the reason why less diffusion occurs across the placenta. No effects on fetus have been noted.[155,156]

About 10% of the drug is excreted unchanged in urine within 24 hours; a glucuronide conjugate is also excreted.

Systemic Effects

The effects of an intravenous infusion of bupivacaine at the rate of 2.0 mg/min for a period of 3 hours produces progressive increases in plasma levels to a mean level of 1.8 mg/mL.[151] These plasma levels are similar to those following regional techniques.[149,150] Such levels have significant effects on cardiovascular function.[151] At plasma concentrations of 1.0 to 2.0 μg/mL, the heart rate increases significantly. Mean arterial blood pressure increased from 87 to 100 mmHg, while the cardiac output decreased about 20%. Plasma epinephrine concentrations increased significantly from 0.03 to 0.08 ng/mL, while plasma norepinephrine levels increased

Naropin™

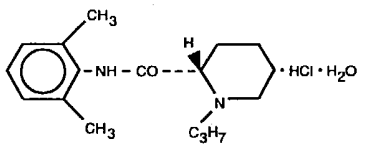
(ropivacaine HCl Injection)

021683R01

DESCRIPTION

Naropin™ (ropivacaine HCl Injection) is a member of the amino amide class of local anesthetics. Naropin injections are sterile, isotonic solutions that contain the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. These solutions are administered parenterally.

Naropin contains ropivacaine HCl which is chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a chemical formula of $C_{17}H_{26}N_2O{\cdot}HCl{\cdot}H_2O$, molecular weight of 328.89 and the following structural formula:



At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 141 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Naropin is preservative free and is available in single dose containers in 2.0, 5.0, 7.5 and 10.0 mg/mL concentrations. The specific gravity of Naropin solutions range from 1.002 to 1.005 at 25°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(-)-enantiomer. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

PHARMACOKINETICS

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition and the vascularity of the administration site.

From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the two phases, (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ±0.3 μg/mL.

Distribution

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α_1-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached (see PRECAUTIONS, Labor and Delivery).

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. Approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 3-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites accounts for less than 3% of dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. Both 3-hydroxy and 4-hydroxy ropivacaine have a local anesthetic activity in animal models less than that of ropivacaine. There is no evidence of *in vivo* racemization in urine of S-(-)-ropivacaine to R-(+)-ropivacaine.

Elimination

The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1.0 h after epidural administration (see Absorption).

Pharmacodynamics

Studies in humans have demonstrated that, unlike most other local anesthetics, the presence of epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on limiting systemic absorption of ropivacaine.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma, progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

In two clinical pharmacology studies (total n=24) ropivacaine and bupivacaine were infused (10 mg/min) in human volunteers until the appearance of CNS symptoms, e.g., visual or hearing disturbances, perioral numbness, tingling and others. Similar symptoms were seen with both drugs. In one study, the mean ± SD maximum tolerated intravenous dose of ropivacaine infused (124 ± 38 mg) was significantly higher than that of bupivacaine (99 ± 30 mg) while in the other study the doses were not different (115 ± 29 mg of ropivacaine and 103 ± 30 mg of bupivacaine). In the latter study, the number of subjects reporting each symptom was similar for both drugs with the exception of muscle twitching which was reported by more subjects with bupivacaine than ropivacaine at comparable intravenous doses. At the end of the infusion, ropivacaine in both studies caused significantly less depression of cardiac conductivity (less QRS widening) than bupivacaine. Ropivacaine and bupivacaine caused evidence of depression of cardiac contractility, but there were no changes in cardiac output.

In nonclinical pharmacology studies comparing ropivacaine and bupivacaine in several animal species, the cardiac toxicity of ropivacaine was less than that of bupivacaine, although both were considerably more toxic than lidocaine. Arrhythmogenic and cardiodepressant effects were seen in animals at significantly higher doses of ropivacaine than bupivacaine. The incidence of successful resuscitation was not significantly different between the ropivacaine and bupivacaine groups.

Clinical Trials

Ropivacaine was studied as a local anesthetic both for surgical anesthesia and for acute pain management. (See DOSAGE and ADMINISTRATION.)

The onset, depth and duration of sensory block are, in general, similar to bupivacaine. However, the depth and duration of motor block, in general, are less than that with bupivacaine.

Epidural Administration In Surgery

There were 25 clinical studies performed in 900 patients to evaluate Naropin epidural injection for general surgery. Naropin was used in doses ranging from 75 to 250 mg. In doses of 100-200 mg, the median (1st-3rd quartile) onset time to achieve a T10 sensory block was 10 (5-13) minutes and the median (1st-3rd quartile) duration at the T10 level was 4 (3-5) hours. (See DOSAGEAND ADMINISTRATION.)

Higher doses produced a more profound block with a greater duration of effect.

Epidural Administration In Cesarean Section

There were 8 studies performed in 218 patients to evaluate Naropin for cesarean section. 5 mg/mL (0.5%) Naropin was used in doses up to 150 mg. Median onset measured at T6 ranged from 11 to 26 minutes. Median duration of sensory block at T6 ranged from 1.7 to 3.2 h, and duration of motor block ranged from 1.4 to 2.9 h. Naropin provided adequate muscle relaxation for surgery in all cases.

Epidural Administration In Labor And Delivery

There were 10 double-blind clinical studies performed to evaluate Naropin versus bupivacaine for epidural block for management of labor pain (Naropin, n=258; bupivacaine, n=231). When administered in doses up to 278 mg as intermittent injections or as a continuous infusion, Naropin produced adequate pain relief.

A prospective meta-analysis on 6 of these studies provided detailed evaluation of the delivered newborns and showed no difference in clinical outcomes compared to bupivacaine. There were significantly fewer instrumental deliveries in mothers receiving ropivacaine as compared to bupivacaine.

LABOR AND DELIVERY META-ANALYSIS: MODE OF DELIVERY

Delivery Mode	Naropin n=199		Bupivacaine n=188	
	n	%	n	%
Spontaneous Vertex	116	58	92	49
Vacuum Extractor	26	)27*	33	)40
Forceps	28		42	
Cesarean Section	29	15	21	11

*p=0.004 versus bupivacaine

Epidural Administration In Postoperative Pain Management

There were 8 clinical studies performed in 382 patients to evaluate Naropin for postoperative pain management after upper and lower abdominal surgery and after orthopedic surgery. The studies utilized intravascular morphine via PCA as a rescue medication and as an efficacy variable. Epidural anesthesia with Naropin was used intraoperatively for each of these procedures prior to initiation of postoperative Naropin. The incidence and intensity of the motor block were dependent on the dose rate of Naropin and the site of injection. Cumulative doses of up to 770 mg of ropivacaine were administered over 24 hours (intraoperative block plus postoperative continuous infusion). The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%). The frequency of motor block was greatest at 4 hours and decreased during the infusion period in all groups. At least 80% of patients in the upper and lower abdominal studies and 42% in the orthopedic studies had no motor block at the end of the 21-hour infusion period. Sensory block was also dose rate-dependent and a decrease in spread was observed during the infusion period. Clinical studies with 2 mg/mL (0.2%) Naropin have demonstrated that infusion rates of 6-10 mL (12-20 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in cases of moderate to severe postoperative pain. In these studies, this technique resulted in a significant reduction in patients' morphine rescue dose-requirement. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

Epidural infusion of Naropin has, in some cases, been associated with transient increases intemperature to > 38.5°C. This occurred more frequently at doses >16 mg/h.

Peripheral Nerve Block

Naropin, 5 mg/mL, (0.5%), was evaluated for its ability to provide anesthesia for surgery using the techniques of Peripheral Nerve Block. There were 13 studies performed including a series of 4 pharmacodynamic and pharmacokinetic studies performed on minor nerve blocks. From these, 235 Naropin treated patients were evaluable for efficacy. Naropin was used in doses up to 275 mg. When used for brachial plexus block, onset depended on technique used. Supraclavicular blocks were consistently more successful than axillary blocks. The median onset of sensory block (anesthesia) produced by ropivacaine 0.5% via axillary block ranged from 10 minutes (medial brachial cutaneous nerve) to 45 minutes (musculocutaneous nerve). Median duration ranged from 3.7 hours (medial brachial cutaneous nerve) to 8.7 hours (ulnar nerve). The 5 mg/mL (0.5%) Naropin solution gave success rates from 56% to 86% for axillary blocks, compared with 92% for supraclavicular blocks.

Local Infiltration

There were 7 clinical studies performed to evaluate the local infiltration of Naropin to produce anesthesia for surgery and analgesia in postoperative pain management. In these studies, 297 patients who received Naropin in doses up to 200 mg were evaluable for efficacy. With infiltration of 100-200 mg Naropin, the time to first request for analgesic was 2-6 hours. When compared to placebo, Naropin produced lower pain scores and a reduction of analgesic consumption.

INDICATIONS AND USAGE

Naropin is indicated for the production of local or regional anesthesia for surgery, for postoperative pain management and for obstetrical procedures.

Surgical Anesthesia:	epidural block for surgery including cesarean section; major nerve block; local infiltration
Acute Pain Management:	epidural continuous infusion or intermittent bolus e.g., postoperative or labor; local infiltration

Standard current textbooks should be consulted to determine the accepted procedures and techniques for the administration of local anesthetic agents.

CONTRAINDICATIONS

Naropin is contraindicated in patients with a known hypersensitivity to Naropin or to any local anesthetic agent of the amide type.

WARNINGS

FOR CESAREAN SECTION, THE 5 MG/ML (0.5%) NAROPIN SOLUTION IN DOSES UP TO 150 MG IS RECOMMENDED. AS WITH ALL LOCAL ANESTHETICS, NAROPIN SHOULD BE ADMINISTERED IN INCREMENTAL DOSES. SINCE NAROPIN SHOULD NOT BE INJECTED RAPIDLY IN LARGE DOSES, IT IS NOT RECOMMENDED FOR EMERGENCY SITUATIONS, WHERE A FAST ONSET OF SURGICAL ANESTHESIA IS NECESSARY. HISTORICALLY, PREGNANT PATIENTS WERE REPORTED TO HAVE A HIGH RISK FOR CARDIAC

ARRHYTHMIAS,CARDIAC/ CIRCULATORY ARREST AND DEATH WHEN BUPIVACAINE WAS INADVERTENTLY RAPIDLY INJECTED INTRAVENOUSLY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINCIANS WHO ARE WELL VERSED IN THE DIAGNOSIS AND MANAGEMENT OF DOSE RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE (WITHOUT DELAY)** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

SOLUTIONS OF NAROPIN SHOULD NOT BE USED FOR THE PRODUCTION OF OBSTETRICAL PARACERVICAL BLOCK ANESTHESIA, RETROBULBAR BLOCK OR SPINAL ANESTHESIA (SUBARACHNOID BLOCK) DUE TO INSUFFICIENT DATA TO SUPPORT SUCH USE. INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK) SHOULD NOT BE PERFORMED DUE TO A LACK OF CLINICAL EXPERIENCE AND THE RISK OF ATTAINING TOXIC BLOOD LEVELS OF NAROPIN.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does *not* ensure against an intravascular or subarachnoid injection.

A well-known risk of epidural anesthesia may be an unintentional subarachnoid injection of local anesthetic. Two clinical studies have been performed to verify the safety of Naropin at a volume of 3 mL injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 15 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes, extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. The results of these two clinical studies showed that a 3 mL dose did not produce any serious adverse events when spinal anesthesia blockade was achieved.

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

PRECAUTIONS

General

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions which contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Administration of higher than recommended doses of Naropin to achieve greater motor blockade or increased duration of sensory blockade may negate the advantages of Naropin's favorable cardiovascular depression profile in the event that an inadvertent intravascular injection occurs.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, and acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Local anesthetics should also be used with caution in patients with hypotension, hypovolemia or heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Because amide-type local anesthetics such as Naropin are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anesthetics are not known to trigger this reaction. However, since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.

Epidural Anesthesia

During epidural administration, Naropin should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When clinical conditions permit, the test dose should contain epinephrine (10 to 15 μg have been suggested) to serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart should be continuously monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic blood pressure. A test dose of a short-acting amide anesthetic such as 30 to 40 mg of lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Use in Head and Neck Area

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Naropin™ (ropivacaine HCl Injection)

Use in Ophthalmic Surgery

The use of Naropin in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of Naropin for such surgery is not recommended.

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Naropin package insert.

Clinically Significant Drug-Drug Interactions

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

In vitro studies indicate that cytochrome P4501A is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. Thus agents likely to be administered concomitantly with Naropin, which are metabolized by this isozyme family may potentially interact with Naropin. Such interaction might be a possibility with drugs known to be metabolized by P4501A2 via competitive inhibition such as theophylline, imipramine and with potent inhibitors such as fluvoxamine and verapamil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals of most local anesthetics, including Naropin, to evaluate the carcinogenic potential have not been conducted.

Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over two generations.

Pregnancy Category B

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects on organogenesis or early fetal development in rats or rabbits. The doses used were approximately equal to 5 and 2.5 times, respectively, the maximum recommended human dose (250 mg) based on body weight. There were no treatment related effects on late fetal development, parturition, lactation, neonatal viability or growth of the offspring in 2 perinatal and postnatal studies in rats, at dose levels up to approximately 5 times the maximum recommended human dose based on body weight. In another study with a higher dose, 23 mg/kg, an increased pup loss was seen during the first 3 days postpartum, which was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate and well-controlled studies in pregnant women of the effects of Naropin on the developing fetus. Naropin should be used during pregnancy only if clearly needed. This does not preclude the use of Naropin after fetal organogenesis is completed or for obstetrical anesthesia or analgesia. (See Labor and Delivery).

Labor and Delivery

Local anesthetics, including Naropin, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia with Naropin for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving Naropin than in those receiving bupivacaine.

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total Naropin dose to which the baby is exposed by breast feeding is far lower than by exposure in utero in pregnant women at term (see PRECAUTIONS).

Pediatric Use

No special studies were conducted in pediatrics. Until further experience is gained in children younger than 12 years, administration of Naropin in this age group is not recommended.

ADVERSE REACTIONS

Reactions to Naropin are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

The reported adverse events are derived from controlled clinical trials in the U.S. and other countries. The reference drug was usually bupivacaine. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 3558 patients enrolled in the clinical trials, 2404 were exposed to Naropin. Each patient was counted once for each type of adverse event.

Incidence >5%

hypotension, fetal bradycardia, nausea, bradycardia, vomiting, paresthesia, back pain

Incidence 1-5%

fever, headache, pain, postoperative complications, urinary retention, dizziness, pruritus, rigors, anemia, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, fetal disorders including tachycardia and fetal distress, and neonatal disorders including jaundice, tachypnea, fever, respiratory disorder and vomiting

A comparison has been made between Naropin and bupivacaine for events with a frequency of 1% or greater. Tables 1a and 1b show adverse events (number and percentage) in patients exposed to *similar doses* in double-blind controlled clinical trials. In the trials, Naropin was administered as an epidural anesthetic/analgesic for surgery, labor, or cesarean section. In addition, patients that received Naropin for peripheral nerve block or local infiltration are included.

Table 1a.
Adverse Events Reported in ≥1% of Adult Patients Receiving Regional Or Local Anesthesia (Surgery, Labor, Cesarean Section, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Naropin total N = 742		Bupivacaine total N = 737	
	N	(%)	N	(%)
hypotension	237	(31.9)	225	(30.5)
nausea	92	(12.4)	96	(13.0)
paresthesia	51	(6.9)	44	(6.0)
vomiting	48	(6.5)	38	(5.2)
back pain	36	(4.9)	47	(6.4)
pain	39	(5.3)	40	(5.4)
bradycardia	32	(4.3)	38	(5.2)
headache	23	(3.1)	26	(3.5)
fever	25	(3.4)	20	(2.7)
chills	16	(2.2)	14	(1.9)
dizziness	18	(2.4)	10	(1.4)
pruritus	16	(2.2)	11	(1.5)
urinary retention	10	(1.3)	12	(1.6)
hypoesthesia	8	(1.1)	10	(1.4)

Table 1b.
Adverse Events Reported in ≥1% of Fetuses or Neonates of Mothers Who Received Regional Anesthesia (Cesarean Section and Labor Studies)

Adverse Reaction	Naropin total N = 337		Bupivacaine total N = 317	
	N	(%)	N	(%)
fetal bradycardia	58	(17.2)	53	(16.7)
neonatal jaundice	12	(3.6)	12	(3.8)
neonatal tachypnea	8	(2.4)	11	(3.5)
fetal tachycardia	7	(2.1)	8	(2.5)
neonatal fever	6	(1.8)	8	(2.5)
fetal distress	4	(1.2)	8	(2.5)
neonatal respiratory distress	5	(1.5)	4	(1.3)
neonatal vomiting	5	(1.5)	1	(0.3)

Incidence <1%

The following list includes all adverse and intercurrent events which were recorded in more than one patient, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Application Site Reactions – injection site pain

Cardiovascular System – vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

Female Reproductive – poor progression of labor, uterine atony

Gastrointestinal System – fecal incontinence, tenesmus

General and Other Disorders – hypothermia, malaise, asthenia, accident and/or injury

Hearing and Vestibular – tinnitus, hearing abnormalities

Heart Rate and Rhythm – extrasystoles, non-specific arrhythmias, atrial fibrillation

Liver and Biliary System – jaundice

Metabolic Disorders – hypokalemia, hypomagnesemia

Musculoskeletal System – myalgia, cramps

Myo/Endo/Pericardium – ST segment changes, myocardial infarction

Nervous System – tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor

Psychiatric Disorders – agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares

Respiratory System – dyspnea, bronchospasm, coughing

Skin Disorders – rash, urticaria

Urinary System Disorders – urinary incontinence, urinary tract infection, micturition disorder

Vascular – deep vein thrombosis, phlebitis, pulmonary embolism

Vision – vision abnormalities

For the indication epidural anesthesia for surgery, the 15 most common adverse events were compared between different concentrations of Naropin and bupivacaine. Table 2 is based on data from trials in the U.S. and other countries where Naropin was administered as an epidural anesthetic for surgery.

Table 2. Common Events (Epidural Administration)

Adverse Reaction	Naropin						Bupivacaine			
	5 mg/mL total N=256		7.5 mg/mL total N=297		10 mg/mL total N=207		5 mg/mL total N=236		7.5 mg/mL total N=174	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)	91	(38.6)	89	(51.1)
nausea	34	(13.3)	68	(22.9)			41	(17.4)	36	(20.7)
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)	32	(13.6)	25	(14.4)
back pain	18	(7.0)	23	(7.7)	34	(16.4)	21	(8.9)	23	(13.2)
vomiting	18	(7.0)	33	(11.1)	23	(11.1)	19	(8.1)	14	(8.0)
headache	12	(4.7)	20	(6.7)	16	(7.7)	13	(5.5)	9	(5.2)
fever	8	(3.1)	5	(1.7)	18	(8.7)	11	(4.7)		
chills	6	(2.3)	7	(2.4)	6	(2.9)	4	(1.7)	3	(1.7)
urinary retention	5	(2.0)	8	(2.7)	10	(4.8)	10	(4.2)		
paresthesia	5	(2.0)	10	(3.4)	5	(2.4)	7	(3.0)		
pruritus			14	(4.7)	3	(1.4)			7	(4.0)

Using data from the same studies, the number (%) of patients experiencing hypotension is displayed by patient age, drug and concentration in Table 4. In Table 3, the adverse events for Naropin are broken down by gender.

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Table 3.
Most Common Adverse Events by Gender (Epidural Administration)
Total N: Females = 405, Males = 355

Adverse Reaction	Female		Male	
	N	(%)	N	(%)
hypotension	220	(54.3)	138	(38.9)
nausea	119	(29.4)	23	(6.5)
bradycardia	65	(16.0)	56	(15.8)
vomiting	59	(14.6)	8	(2.3)
back pain	41	(10.1)	23	(6.5)
headache	33	(8.1)	17	(4.8)
chills	18	(4.4)	5	(1.4)
fever	16	(4.0)	3	(0.8)
pruritus	16	(4.0)	1	(0.3)
pain	12	(3.0)	4	(1.1)
urinary retention	11	(2.7)	7	(2.0)
dizziness	9	(2.2)	4	(1.1)
hypoesthesia	8	(2.0)	2	(0.6)
paresthesia	8	(2.0)	10	(2.8)

Table 4.
Effects of Age on Hypotension (Epidural Administration)
Total N: Naropin = 760, bupivacaine = 410

	Naropin						Bupivacaine			
AGE	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<65	68	(32.2)	99	(43.2)	87	(51.5)	64	(33.5)	73	(48.3)
≥65	31	(68.9)	47	(69.1)	26	(68.4)	27	(60.0)	16	(69.6)

Systemic Reactions

The most commonly encountered acute adverse experiences that demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production or competition with other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the route of administration and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1 % of local anesthetic administrations.

Cardiovascular System Reactions

High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic Reactions

Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (see WARNINGS). These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Neurologic Reactions

The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose and concentration of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the drug.

During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. These observations may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, loss of bladder and bowel control (fecal and urinary incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of subarachnoid block typically start within 2-3 minutes of injection. Doses of 15 and 22.5 mg of Naropin resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes and extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. Other neurological effects following unintentional subarachnoid administration during epidural anesthesia may include persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery. Headache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported (see DOSAGE AND ADMINISTRATION discussion of Lumbar Epidural Block). A high spinal is characterized by paralysis of the arms, loss of consciousness, respiratory paralysis and bradycardia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies

The practitioner should be familiar with standard contemporary textbooks that address the management of local anesthetic emergencies. No specific information is available on the treatment of overdosage with Naropin; treatment should be symptomatic and supportive. Therapy with Naropin should be discontinued.

The first consideration is prevention, best accomplished by incremental injection of Naropin, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

The mean dosages of ropivacaine producing seizures, after intravenous infusion in dogs, nonpregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5.0 μg/mL, respectively. In rats, the LD_{50} is 9.9 and 12 mg/kg by the intravenous route for males and females respectively.

In human volunteers given intravenous Naropin, the mean maximum tolerated total and free arterial plasma concentrations were 4.3 and 0.6 μg/mL respectively, at which time moderate CNS symptoms (muscle twitching) were noted.

Clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated, endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask.

The supine position is dangerous in pregnant women at term because of aorta-caval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non-pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3-5 mL of a short acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered. For specific techniques and procedures, refer to standard contemporary textbooks.

Dosage Recommendations

	Conc. mg/mL (%)	Volume mL	Dose mg	Onset min	Duration hours
SURGICAL ANESTHESIA					
Lumbar Epidural Administration	5.0 (0.5%)	15-30	75-150	15-30	2-4
Lumbar Epidural Administration	7.5 (0.75%)	15-25	113-188	10-20	3-5
Surgery	10.0 (1.0%)	15-20	150-200	10-20	4-6
Lumbar Epidural Administration Cesarean Section	5.0 (0.5%)	20-30	100-150	15-25	2-4
Thoracic Epidural Administration To establish block for postoperative pain relief	5.0 (0.5%)	5-15	25-75	10-20	n/a[1]
Major Nerve Block (e.g., brachial plexus block)	5.0 (0.5%)	35-50	175-250	15-30	5-8
Field Block (e.g., minor nerve blocks and infiltration)	5.0 (0.5%)	1-40	5-200	1-15	2-6
LABOR PAIN MANAGEMENT					
Lumbar Epidural Administration					
Initial Dose	2.0 (0.2%)	10-20	20-40	10-15	0.5-1.5
Continuous infusion[2]	2.0 (0.2%)	6-14 mL/h	12-28 mg/h	n/a[1]	n/a[1]
Incremental injections (top-up)[2]	2.0 (0.2%)	10-15 mL/h	20-30 mg/h	n/a[1]	n/a[1]
POSTOPERATIVE PAIN MANAGEMENT					
Lumbar Epidural Administration					
Continuous infusion[3]	2.0 (0.2%)	6-10 mL/h	12-20 mg/h	n/a[1]	n/a[1]
Thoracic Epidural Administration Continuous infusion[3]	2.0 (0.2%)	4-8 mL/h	8-16 mg/h	n/a[1]	n/a[1]
Infiltration (e.g., minor nerve block)	2.0 (0.2%)	1-100	2-200	1-5	2-6
	5.0 (0.5%)	1-40	5-200	1-5	2-6

1 = Not Applicable
2 = Median dose of 21 mg per hour was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.
3 =Cumulative doses up to 770 mg of Naropin over 24 hours for postoperative pain management have been well tolerated in adults.

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The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Experience to date indicates that a cumulative dose of up to 770 mg Naropin administered over 24 hours is well tolerated in adults when used for postoperative pain management.

For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intraoperatively, then an epidural block with Naropin is induced via an epidural catheter. Analgesia is maintained with an infusion of Naropin, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6-10 mL (12-20 mg), per hour provide adequate analgesia with only slight and nonprogressive motor block in cases of moderate to severe postoperative pain. If patients require additional pain relief, higher infusion rates of up to 14 mL (28 mg) per hour may be used. With this technique a significant reduction in the need for opioids was demonstrated. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

HOW SUPPLIED

Naropin™ Astra E-Z OFF® Single Dose Vials:		
7.5 mg/mL	10 mL	NDC 0186-0867-41
10.0 mg/mL	10 mL	NDC 0186-0868-41
Naropin™ Single Dose Vials:		
2.0 mg/mL	20 mL	NDC 0186-0859-51
5.0 mg/mL	30 mL	NDC 0186-0863-61
7.5 mg/mL	20 mL	NDC 0186-0867-51
10.0 mg/mL	20 mL	NDC 0186-0868-51
Naropin™ Single Dose Ampules:		
2.0 mg/mL	20 mL	NDC 0186-0859-52
5.0 mg/mL	30 mL	NDC 0186-0863-62
7.5 mg/mL	20 mL	NDC 0186-0867-52
10.0 mg/mL	20 mL	NDC 0186-0868-52
Naropin™ Single Dose Infusion Bottles:		
2.0 mg/mL	100 mL	NDC 0186-0859-81
2.0 mg/mL	200 mL	NDC 0186-0859-91
Naropin™ Sterile-Pak® Single Dose Vials:		
2.0 mg/mL	20 mL	Product Code 0859-59
5.0 mg/mL	30 mL	Product Code 0863-69
7.5 mg/mL	20 mL	Product Code 0867-59
10.0 mg/mL	20 mL	Product Code 0868-59
Naropin™ Polyamp DuoFit™ Sterile Pak®:		
2.0 mg/mL	10 mL	NDC 0186-0859-47
2.0 mg/mL	20 mL	NDC 0186-0859-57
5.0 mg/mL	10 mL	NDC 0186-0863-47
5.0 mg/mL	20 mL	NDC 0186-0863-57
7.5 mg/mL	10 mL	NDC 0186-0867-47
7.5 mg/mL	20 mL	NDC 0186-0867-57
10.0 mg/mL	10 mL	NDC 0186-0868-47
10.0 mg/mL	20 mL	NDC 0186-0868-57

The solubility of ropivacaine is limited at pH above 6. Thus care must be taken as precipitation may occur if Naropin is mixed with alkaline solutions.

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the ampule or vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use. When a container is required to have a sterile outside, a Sterile-Pak should be chosen. Glass containers may, as an alternative, be autoclaved once. Stability has been demonstrated using a targeted F_0 of 7 minutes at 121°C.

Solutions should be stored at controlled room temperature 20° – 25°C (68° – 77°F) [see USP].

These products are intended for single use and are free from preservatives. Any solution remaining from an opened container should be discarded promptly. In addition, continuous infusion bottles should not be left in place for more than 24 hours.

Rx only

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ASTRA® Astra USA, Inc.
Westborough, MA 01581

INTRODUCTION TO ANESTHESIA

David L. Longnecker
Eric A. Murphy

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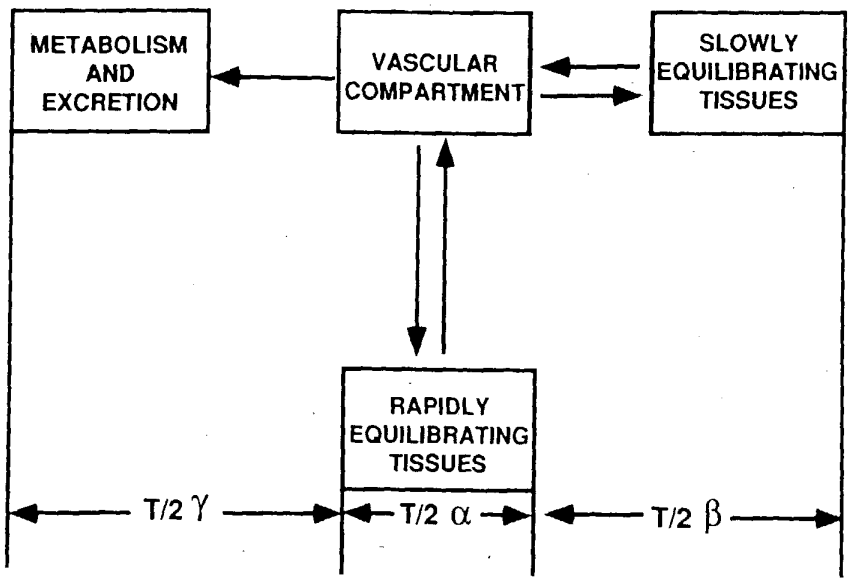

Figure 17-7

Pharmacokinetic phases according to a three-compartment model.
(Reprinted by permission from Covino BG, Vassalo HG, Local Anesthetics: Mechanism of Action and Clinical Use. *New York: Grune & Stratton, 1976, p 110.)*

rate, and mepivacaine somewhat more slowly. Clearance rates of amide local anesthetics are identical to their rates of hepatic metabolism, since direct renal elimination is negligible.

The disposition of local anesthetics depends on the patient's age and health. The elimination half-life of lidocaine in patients 22 to 26 years of age is 81 minutes, compared with 139 minutes in patients 61 to 71 years of age. The elimination of lidocaine may be slowed several-fold in patients with liver disease. Although single-injection techniques tend to be safe in these patients, the administration of additional local anesthetic must be curtailed to account for the slow disposition of the drug.

Choosing a Local Anesthetic Mixture

Table 17-4 lists the local anesthetics and their primary uses (injection sites). As a rule, the actions of the many available local anesthetics are more alike than they are different; almost any local anesthetic can be made to work for any kind of regional anesthesia. In practice, it is best to employ a small number of drugs whose pharmacologic properties are well understood. When there are special advantages to particular local anesthetics, the choice depends on the planned nerve block, duration of anesthesia, speed of onset, and potential toxicity.

■ Local Anesthetics for Specific Nerve Blocks

Neurologic complications after spinal anesthesia are rare but devastating. For this reason, practitioners use only a small number of drugs with well-established records for safe use in spinal anesthesia. These include tetracaine, lidocaine, and bupivacaine in hyperbaric, isobaric, and hypobaric formulations. Additives are limited to preservative-free opioids and epinephrine, which is added to prolong duration. The dose of epinephrine (200 μg) is chosen to yield an expected concentration of 5 μg/ml when diluted in the 40 ml of cerebrospinal fluid (CSF) in the lumbosacral region of an adult. There is no need to add sodium bicarbonate to increase the pH of the solution because the small amount of drug is effectively buffered by the CSF into which it is injected.

Table 17-4

Uses of Common Local Anesthetics

Agent	Uses
Cocaine	Topical
Procaine	Infiltration
	Differential spinal
	Spinal
Chloroprocaine	Brachial plexus
	Epidural
Lidocaine	Topical
	Infiltration
	IV regional
	Brachial plexus
	Spinal
	Epidural
Mepivacaine	Infiltration
	Brachial plexus
	Spinal
	Epidural
Prilocaine	Infiltration
	IV regional
	Brachial plexus
	Epidural
Bupivacaine	Infiltration
	Brachial plexus
	Epidural
	Spinal
Etidocaine	Infiltration
	Epidural
Tetracaine	Topical
	Spinal
Ropivacaine	Infiltration
	Brachial plexus
	Epidural
	Spinal

For epidural anesthesia, bupivacaine and lidocaine are most popular, although chloroprocaine and etidocaine are used occasionally. Additives include preservative-free opioids and epinephrine, usually in the amount of 5 μg/ml of local anesthetic solution. In contrast to the small doses employed in spinal anesthesia, epidural anesthesia requires much greater quantities of local anesthetics, whose actions are improved by the addition of sodium bicarbonate (see below).

For peripheral neural blocks, lidocaine, bupivacaine, and mepivacaine are popular. Additives include vasoconstrictors and sodium bicarbonate.

■ Duration of Blockade

On first consideration, it might seem best to choose local anesthetics to provide the longest possible duration of effect so as to delay as long as possible the onset of postoperative pain. There are significant disadvantages to this practice. First, the molecular properties that confer long action on local anesthetics (protein binding) also imply slow onset of action, which is a major obstacle to the practical use of regional anesthesia. Second, prolonged anesthesia with paralysis may delay recovery and discharge from the recovery room when a patient undergoes an outpatient operation. Third, delayed recovery from the anesthetic hinders prompt postoperative evaluation of possible neurologic damage (from the operation or the anesthetic), compartment syndromes, or tight plaster casts. Fourth, bladder distension and failure to void are common complications exacerbated by prolonged spinal or epidural anesthesia. Thus most practitioners choose a local anesthetic drug with the goal of providing surgical anesthesia that exceeds the duration of the operation only by enough time to allow for reasonable operative delays. A catheter, such as used in continuous spinal, epidural, or brachial plexus anesthesia, permits reinjecting local anesthetic and controlling the duration of the anesthesia.

■ Improving Onset of Anesthesia: Carbonation and Bicarbonate

The slow onset of anesthesia with bupivacaine and other long-acting drugs (30 minutes or longer to full effect) may require that the block be performed outside the operating room in a patient holding area. Although such holding areas are convenient, they are not always available. Choosing a faster-acting drug such as lidocaine or mepivacaine is the most direct approach to this problem. When this is not possible, other methods can be used to speed the onset of regional anesthesia.

Because diffusion of the local anesthetic into the interior of the axon depends on the unionized lipophilic base, the onset of anesthesia can be hastened by adding CO_2 to the local anesthetic (carbonating) or by increasing its pH with sodium bicarbonate. CO_2 from carbonated solutions diffuses across the nerve membrane, thereby increasing the intracellular hydrogen ion concentration. This in turn increases the fraction of intracellular local anesthetic that is protonated, or charged, and is unable to diffuse back out of the neuron. This "ion trapping" produces a more profound block more rapidly, as compared with that produced by uncarbonated formulations of local

Table 17-5

Amount of Sodium Bicarbonate for Alkalinization of Local Anesthetic Solutions

Local Anesthetic (pK_a)	HCO_3^- Required (mEq/20 ml)
Chloroprocaine 3% (8.7)	1.92
Mepivacaine 1.5% (7.6)	1.92
Etidocaine 1% to 1.5% (7.7)	0.048
Bupivacaine 0.25% (8.1)	0.024
Lidocaine 1% to 2% (7.9)	1.92

anesthetic. Carbonated local anesthetics are only available commercially in Canada and some European countries.

The usual anesthetic solution is manufactured to have a pH of 3.5 to 6.5 to enhance shelf life and solubility. Adding sodium bicarbonate brings the pH of the solution closer to the pK_a of the local anesthetic, thereby increasing the relative concentration of the uncharged form of the molecule and shortening latency. Increasing the pH too much causes precipitation of the relatively insoluble free base. Solutions of chloroprocaine and lidocaine can be brought to near physiologic pH without precipitation. Delayed precipitation occurs in mepivacaine solutions above neutral pH. Bupivacaine and etidocaine solutions form precipitates after the addition of small amounts of sodium bicarbonate and cannot be alkalinized to physiologic pH. These more alkaline solutions of local anesthetics also cause less pain when used for local infiltration (Table 17-5).

Local anesthetic solutions manufactured with epinephrine are supplied at a pH of 3.5 to prevent oxidation of the epinephrine. The speed of onset of anesthesia is greatly improved by increasing the pH of these solutions. An alternative is to purchase local anesthetic solutions manufactured without added epinephrine, which are typically less acid, and adding the epinephrine just before injection, but objective clinical studies demonstrate that premixed solutions can result in rapid onset of analgesia when sodium bicarbonate is added prior to injection.

Toxicity of Local Anesthetic Agents

Local anesthetics produce few side effects when given in an appropriate dose at the proper site. Most toxic reactions occur after the accidental intravascular injection of a large dose of local anesthetic, although an excessive dose given into an appropriate anatomic location can lead to systemic toxicity.

■ Systemic Toxicity

Systemic effects of local anesthetics occur when the drugs reach the circulation from the site of injection. When they are mistakenly injected in large doses into an artery or vein and the anesthetic appears in the blood as a bolus, a catastrophic combination of seizures, coma, arrhythmias, and cardiac arrest can occur. When the blood concentration of local anesthetic increases more slowly due to uptake from tissue, there appears gradually a characteristic spectrum of effects, each representing a specific concentration of anesthetic. Aside from methemoglobinemia and other minor effects specific to individual drugs, these systemic effects all result from interference with sodium channels in electrically excitable membranes in the heart and the nervous system.

Central Nervous System Toxicity

Toxic effects of local anesthetics occur in the central nervous system (CNS) at lesser blood concentrations than are required to produce cardiovascular toxicity; therefore, CNS toxicity appears earlier than cardiovascular toxicity in the typical clinical course of a toxic reaction that follows slow uptake of drug. In the order of appearance, these CNS signs and symptoms consist of lightheadedness, dizziness, a metallic taste in the mouth, numbness of the tongue or lips, slurred speech, tinnitus, agitation, seizures, sedation, and coma (Table 17-6). The seizures appear to be due

Table 17-6

Signs and Symptoms of Local Anesthetic-Induced CNS Toxicity

Initial events
Tinnitus
Lightheadedness
Confusion
Circumoral numbness
Excitation phase
Tonic-clonic convulsions
Depression phase
Unconsciousness
Generalized CNS depression
Respiratory arrest

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Lidocaine and Bupivacaine Mixtures for Epidural Blockade

L. T. Seow, F.F.A.R.A.C.S., F. J. Lips, F.F.A.R.A.C.S., M.R.C.P. (UK),†*
M. J. Cousins, M.D., F.F.A.R.A.C.S.,‡ L. E. Mather, Ph.D.§

In a prospective double-blind clinical study, single-dose lumbar epidural blockade was instituted in 60 healthy patients undergoing lower abdominal surgery. Patients were randomly assigned to one of five groups. Each group received treatment with a different local anesthetic solution containing 1:200,000 epinephrine. Local anesthetic solutions used were 0.5 per cent bupivacaine HCl, 2 per cent lidocaine HCl, and lidocaine–bupivacaine mixtures in the ratios of 1:3, 1:1 or 3:1 by volume. Onset and complete spread of sensory blockade were similar in all five groups. Time to regression to two segments of partial and complete sensory blockade was positively correlated ($P < 0.05$) with increasing dose of bupivacaine in the solutions and ranged from 84 min (partial) and 70 min (complete) for lidocaine, to 128 min (partial) and 101 min (complete) for bupivacaine. Using skin temperature as a criterion of sympathetic blockade, all three mixtures demonstrated a duration of action intermediate between the two single drugs, lidocaine (124 ± 13 min) and bupivacaine (286 ±32 min). Onset of complete motor blockade was fastest and the degree of motor blockade was most profound with the mixture containing equal proportions of lidocaine and bupivacaine. Pharmacokinetics of individual drugs were unaltered in any of the mixutres. (Key words: Anesthetics, local: bupivacaine; lidocaine; mixtures. Anesthetic techniques: epidural. Pharmacokinetics.)

USED ALONE, bupivacaine has acquired a reputation for slow onset[1-3]. Hence, in a busy operating schedule, it would seem attractive to use an agent having the characteristics of fast onset while still retaining the desirable long-duration characteristics of bupivacaine. At first, it appeared that etidocaine would fulfill this requirement.[4] However, experience with etidocaine has revealed its propensity for producing prolonged motor blockade and this feature is not always desirable.[5,6] Consequently, there has been a resurgence of interest in mixtures of local anesthetic agents to combine the desirable properties of each component. Earlier animal studies[7] indicated that it may be possible to retain the favorable characteristics of each component of such mixtures, and *in vitro* studies are in agreement, provided that *p*H and concentration of the final solution are adjusted appropriately.[8]

Previous clinical studies of mixtures of local anesthetic agents have produced inconsistent findings. The advantage of shortening the latency of the long-acting local anesthetic agent bupivacaine by adding chloroprocaine[9] or carbonated lidocaine[10] has been demonstrated for brachial plexus blockade. Others have prolonged the duration of action of short-acting local anesthetics by adding tetracaine for peripheral nerve blockade.[11] However, the clinical advantages of mixing local anesthetics for epidural blockade have not been demonstrated clearly. Whereas, tetracaine prolonged the duration of analgesia from lidocaine, chloroprocaine, and mepivacaine,[11] analgesia from a mixture of bupivacaine and chloroprocaine did not last significantly longer than that from chloroprocaine alone.[12]

To date, there has been no controlled clinical study of the clinical effects and pharmacokinetics of mixtures of amide local anesthetics. The present study provides an objective clinical examination combined with a pharmacokinetic study of two commonly used local anaesthetics, lidocaine and bupivacaine, alone and mixed together.

Materials and Methods

STUDY PLAN

Using a double-blind method, clinical effects and pharmacokinetics were studied after epidural injection of either 2 per cent lidocaine HCl or 0.5 per cent bupivacaine HCl alone, or of any of three different mixtures of the two agents, all solutions containing 1:200,000 epinephrine. The subjects of the study were 60 healthy patients classified ASA I or II and undergoing lower abdominal surgery. After a detailed explanation of the protocol, ¶ informed written consent was obtained on the night before surgery. Twelve patients were allocated randomly into five groups, each group receiving a different local anesthetic solution. The composition of the local anesthetic solutions tested and the characteristics of the patients studied are shown in table 1.

PATIENT PREPARATION AND ASSESSMENT

Each patient was premedicated with 10 mg diazepam orally two hours before surgery. Prior to commencing the epidural block, an intravenous cannula was inserted and one liter of balanced saline solution was administered by the time surgery commenced. In the opposite arm, a

* Senior Registrar.
† Senior Staff Specialist.
‡ Professor and Chairman.
§ Senior Lecturer.
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Address reprint requests to Dr. Michael J. Cousins.

¶ The study was approved by the Committee on Clinical Investigation of the Flinders Medical Centre.

TABLE 1. Composition of Local Anesthetic Solutions and Characteristics of Patients Assigned to Each Group

Group	4L*	3L:1B	2L:2B	1L:3B	4B
Local Anesthetic Solution					
2 per cent lidocaine HCl (ml)	20	15	10	5	0
0.5 per cent bupivacaine HCl (ml)	0	5	10	15	20
*p*H of mixture	4.0	3.9	3.8	3.7	3.6
Patient Characteristics†					
Age (years)	45 (15)	54 (15)‡	37 (11)	37 (9)	32 (10)
Weight (kg)	62 (12)	74 (10)‡	61 (9)	64 (14)	63 (9)
Height (cm)	165 (10)	172 (12)	167 (11)	162 (11)	164 (9)
Operation duration (min)	43 (3)	48 (3)	48 (3)	49 (2)	45 (3)

* All solutions contain 1:200,000 epinephrine.
† Mean (SD).
‡ Significantly different to other groups ($P < 0.05$).

central venous catheter was inserted so that by measurement, its tip was in the subclavian vein. This was used for sampling blood for pharmacokinetic purposes. Blood pressure was recorded by sphygmomanometry and pulse rate by palpation, prior to, and every 5 min following, the epidural injection. Mean arterial pressure (MAP) was derived from diastolic pressure plus 1/3 pulse pressure. Two thermistor probes were taped to the plantar surface of each great toe and connected to a two-channel telethermometer with chart recorder to monitor the progress of sympathetic blockade.

With the patient in either the right or left lateral position, an anesthesiologist administered the epidural blockade at the L1–2 interspace, using a single-dose technique. Local anesthetic solutions were mixed at the bedside from commercially available epinephrine-containing solutions (table 1). A standardized volume of the 20 ml local anesthetic solution was administered via the 18swg Tuohy needle at a rate of 1 ml/s and with the bevel of the needle facing caudally. The patient was then turned supine and a separate assessor, who was unaware of which drug was injected, commenced clinical observations of sensory and motor blockade.

Sensory Blockade

Sensory blockade at each dermatome was assessed every 2 min for 20 min and then every 5 min until surgery commenced at 40 min. Partial sensory blockade was defined as loss of pin prick sensation, and complete sensory blockade as loss of touch sensation. Latency of onset was defined as follows: initial—the time at which sensory blockade occurred at any one dermatome bilaterally; ±4 segments—the time at which 4 segments above and below the level of injection were blocked (as an index of readiness for surgery); complete—the time at which no further progression of blockade occurred; and S1—the time at which blockade occurred of the dermatome over the lateral aspect of the foot and little toe.

Duration of sensory blockade was recorded as follows: ±2 segment regression—time from complete spread to regression of 2 dermatomes; ±4 segment regression—time from onset of sensory blockade in 4 segments to regression of the same; and duration of each dermatome blocked from onset to offset.

Motor Blockade

Motor blockade in the lower limbs was assessed every 5 min as above by testing power of a specific joint movement of both lower limbs which were regarded as equivalent to the following myotomes: L2—hip flexion; L3—knee extension; L4—ankle dorsiflexion; L5—big toe dorsiflexion; and S1—ankle plantar flexion.

This was regarded as the most practical, albeit indirect, assessment of accompanying abdominal muscle relaxation. Time to onset of partial motor blockade was defined as time to any reduction in power, complete motor blockade as absent power at a myotome, and intensity of motor blockade was recorded as myotome score, which was the number of myotomes blocked from 0 to maximal 10 (*i.e.*, 5 myotomes in each lower limb).

Forty-five minutes after epidural blockade, light general anesthesia was induced with 1 mg/kg iv methohexitone and maintained with 4:2 l/min nitrous oxide/oxygen and 0.5 per cent halothane, with patients breathing spontaneously through a Mapleson A circuit.

Postoperatively, clinical evaluation of sensory and motor profiles were continued in the recovery room at 15-min intervals for a further period of four hours or until return of sensory and motor functions, whichever occurred earlier.

PHARMACOKINETIC STUDIES

Blood samples for pharmacokinetic studies were obtained prior to and at 5 min intervals for 45 min, after the epidural blockade. Lidocaine and bupivacaine blood concentrations were determined with the gas chromatographic technique of Mather and Tucker,[13] using a nitrogen selective detector and mepivacaine as the internal standard. From these data, maximum blood concentra-

tions (C_{max}) and the times at which C_{max} occurred (T_{max}) were determined by inspection. The areas under the blood concentration time curves from 0 to 45 min (AUC) were determined by application of the trapezoidal rule using a digital computer. Because different amounts of agents were injected between groups, comparisons of C_{max} and AUC were adjusted for mass of each component injected.

Statistical Analysis

Data analysis was performed on a digital computer (Digital Equipment Corporation DEC-10®) using the Statistical Package for the Social Sciences[14] and nonparametric methods. Specifically, Kruskal-Wallis analysis of variance was used to examine inter- and intragroup variability and the Spearman correlation test was used to examine variables as a function of the concentrations of components. A probability of $P < 0.05$ was regarded as statistically significant.

Results for the variables have been reported as mean and standard deviation to facilitate calculated comparisons between groups.

Results

Patient Variables

There were no significant differences in the mean height of patients or the duration of surgery among the five groups (table 1). In spite of random allocation, both the mean age and weight of Group 3L:1B were significantly greater than the other groups. Therefore, age and weight were used as covariates in the analysis of data but there was no change in the statistical outcome when these parameters were excluded as covariates.

Sensory Blockade

There were no significant differences among the five groups for time to onset of partial and complete sensory blockade (fig. 1, table 2) or for number of dermatomes blocked at 40 min after injection. The duration of partial sensory blockade of segments T11–S5 was significantly longer for Group 4B, as was the duration of complete sensory blockade of segments T11–L5 and S3–S5. The duration of both partial and complete sensory blockade correlated with the fractional dose of bupivacaine in the solution (table 3).

Motor Blockade

Among the five groups, there was no significant difference in latency of partial motor blockade. However the latency of complete motor blockade was significantly longer in Group 1L:3B (table 4). Mean myotome score for complete motor blockade was greatest with Group 2L:2B but least with Group 1L:3B, during the period from 15 to 35 min after administration of the epidural blockade (fig. 2). Group 1L:3B consistently had the greatest mean myotome score for partial motor blockade at all time intervals from 15 min to 4 h postoperatively, although statistical significance ($P < 0.05$) was only obtained in half of these time intervals.

Sympathetic Blockade

The times of onset and the magnitude of the rise in the temperature of the great toe were similar in all five groups (table 5). However, the duration of the maximum rise in temperature was significantly longer in Group 4B, shortest in Group 4L, and intermediate in the three mixtures.

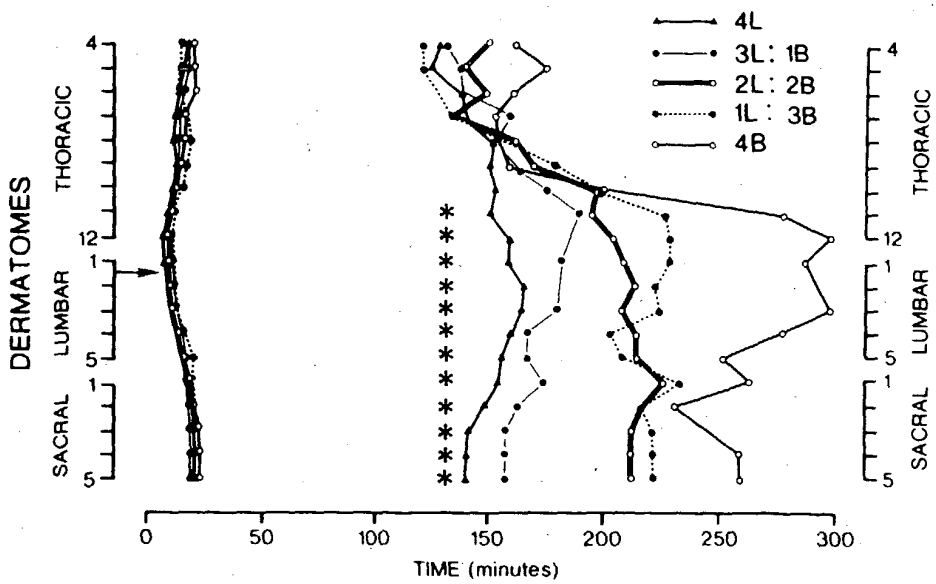

FIG. 1. Mean time-segment diagram for partial sensory blockade at each dermatome level. Data points plotted are mean values. (→) = site of injection of local anesthetics. *Denotes significant difference among groups ($P < 0.05$). A similar time-segment diagram for complete sensory blockade was obtained.

TABLE 2. Onset of Bilateral Sensory Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	P*
Partial Sensory Block‡						
Initial onset (min)	6 (3)	7 (4)	6 (3)	7 (2)	5 (2)	NS†
±4 segments spread (min)	13 (8)	12 (4)	15 (8)	16 (7)	12 (5)	NS†
Complete spread (min)	26 (9)	23 (7)	30 (10)	27 (11)	27 (8)	NS†
S1 block onset (min)	16 (9)	14 (7)	14 (11)	15 (7)	14 (10)	NS†
Complete Sensory Block‡						
Initial onset (min)	12 (6)	9 (5)	10 (6)	14 (6)	16 (11)	NS†
±4 segment spread (min)	25 (12)	14 (5)	26 (14)	33 (12)	26 (17)	NS†
Complete spread (min)	35 (9)	32 (8)	36 (9)	37 (10)	39 (8)	NS†
S1 block onset (min)	30 (14)	24 (4)	24 (18)	37 (6)	30 (14)	NS†
Number of patients with complete S1 blockade	3	6	4	3	3	

* Probability of significant difference among groups (Kruskal-Wallis test).
† No significant difference among the groups ($P > 0.05$).
‡ Mean (SD).

HEMODYNAMICS

In each group, mean arterial pressure (MAP) was reduced significantly following epidural blockade, the maximum decrease being greatest for group 3L:1B (table 5). However, the lowest MAP after the block was not significantly different from that following the induction of general anesthesia. Heart rate did not differ significantly among the five groups following the epidural blockade but decreased 15 per cent following induction of anesthesia.

PHARMACOKINETICS

When the individual values of C_{max} were adjusted for each 100 mg of agent injected, there were no significant differences between the groups. However T_{max} and AUC (per 100 mg) were weakly inversely correlated with the fraction of bupivacaine in the mixtures (Spearmans r −0.37 [$P < 0.02$] and −0.24 [$P < 0.02$], respectively, table 6).

Discussion

Two important findings have emerged from this study. First, it was found that epidural injection of mixtures of lidocaine and bupivacaine resulted in no substantial advantage over either agent alone. Second, maximum blood concentrations associated with the various mixtures of lidocaine and bupivacaine were the same as if the components had been injected individually.

The finding that time to onset of sensory blockade did not differ among the local anesthetic mixtures was in agreement with an analogous study of epidural anesthesia using chloroprocaine–bupivacaine mixtures.[12] In the present study, the number of spinal segments with sensory block at 40 min postinjection did not differ among the groups. Delay in onset of complete blockade of the large S1 root[15] was similar in all groups. Although partial sensory block of S1 was obtained in all patients, only a few patients in each group had complete sensory and motor blockade of S1. Thus, when safe doses of local anesthetic were injected into the epidural space via the needle, the onset of sensory blockade was as rapid for bupivacaine as for lidocaine. This suggests that bulk flow and rapid transfer of amide local anesthetics into spinal fluid, perhaps via arachnoid granulations in dural cuff regions, is the major determinant of onset of action.[16] Alternatively, local ischemia exerted by epinephrine has an overwhelming influence and nullifies the individual characteristics of the agents.[16] However, when smaller

TABLE 3. Duration of Sensory Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	r*
2 Segment Regression†						
Partial (min)	84 (45)	99 (27)	98 (31)	108 (33)	138 (68)	0.38‡
Complete (min)	76 (30)	73 (29)	89 (35)	77 (33)	113 (51)	0.22‡
±4 Segment Regression†						
Partial (min)	132 (64)	140 (21)	151 (67)	147 (57)	168 (44)	0.22‡
Complete (min)	100 (55)	81 (26)	100 (46)	79 (19)	135 (48)	0.17‡

* r Spearman nonparametric correlation coefficient for duration with increasing dose of bupivacaine.
† Mean (SD).
‡ $P < 0.05$.

TABLE 4. Times to Onset of Bilateral Motor Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	P*
Partial Motor Block†						
Initial onset (min)	8 (3)	13 (7)	10 (3)	16 (10)	14 (10)	NS‡
Complete spread (min)	27 (14)	25 (7)	27 (10)	28 (14)	27 (14)	NS‡
S1 onset (min)	25 (14)	25 (14)	19 (10)	34 (24)	28 (17)	NS‡
Number of patients with partial S1 blockade	4	5	7	4	4	
Complete Motor Block†						
Initial onset (min)	16 (7)	18 (7)	15 (7)	28 (14)	19 (3)	0.01
Complete spread (min)	35 (10)	26 (10)	24 (14)	36 (14)	29 (14)	NS‡
S1 onset (min)	40	35 (14)	24 (14)	—	45	NS‡
Number of patients with complete S1 blockade	1	2	4	0	1	

* Probability of significant difference among groups (Kruskal-Wallis test).

† Mean (SD).

‡ No significant difference among the groups ($P > 0.05$).

doses are injected epidurally, differences between agents have been detected by comparing the time of onset of blockade of the S1 outflow.[17,18]

It would not have been surprising if the duration of sensory blockade had been positively correlated with the dose of bupivacaine in the local anesthetic mixture. However, the correlation was so weak so that the only group with a distinct prolongation of sensory blockade was that where bupivacaine alone was used. These findings support those of Moore *et al.*[11] who reported increased duration of analgesia when tetracaine crystals were added to lidocaine solution to make a mixture of approximately 1:3.

Degree of motor blockade sufficient for abdominal surgery can be achieved by epinephrine-containing solutions of 2 per cent lidocaine, 1.5 percent etidocaine, or 0.75 per cent bupivacaine. However, persistence of motor blockade into the postoperative period, particularly after surgery of short duration, is undesirable. Thus, mixtures of 2 per cent lidocaine and 0.5 per cent bupivacaine theoretically could retrain the high degree of motor blockade of lidocaine for the duration of surgery and the longer analgesic property of bupivacaine for postoperative analgesia. In this study, the mixture containing equal proportions by volume of 2 per cent lidocaine and 0.5 per cent bupivacaine resulted in a greater number of myotomes with complete motor blockade between 15 and 40 min after injection, as well as the highest frequency of S1 motor blockade. Therefore, this mixture would appear to be useful for a single-dose epidural blockade where motor paralysis is required for the operative procedure followed by some residual postoperative analgesia.

Duration of blockade of sympathetic vasoconstrictor fibers was similar for all three mixtures but lidocaine alone was of significantly shorter duration than bupivacaine alone. Blood pressure and heart rate decreased following epidural blockade in all five groups, presumably reflecting sympathetic blockade. Subsequent induction of light general anesthesia resulted in no further change in blood pressure and this is in keeping with previous studies of epidural blockade and light general anesthesia.[19] However, pulse rate was decreased significantly after general anesthesia. This may have been due to the negative chronotropic effect of halothane, in addition to epidural sympathetic blockade.

In a previous pharmacokinetic study of a mixture of ester and amide local anesthetics chloroprocaine and bupivacaine, Raj *et al.* reported that the T_{max} values of the components were separated widely but for a mixture of the amides, lidocaine, and bupivacaine, similar values of T_{max} resulted.[20] Recent blood concentration data obtained with a specific assay for chloroprocaine[21] have invalidated the conclusion regarding the amide-ester mixture. However, the current study agrees with the

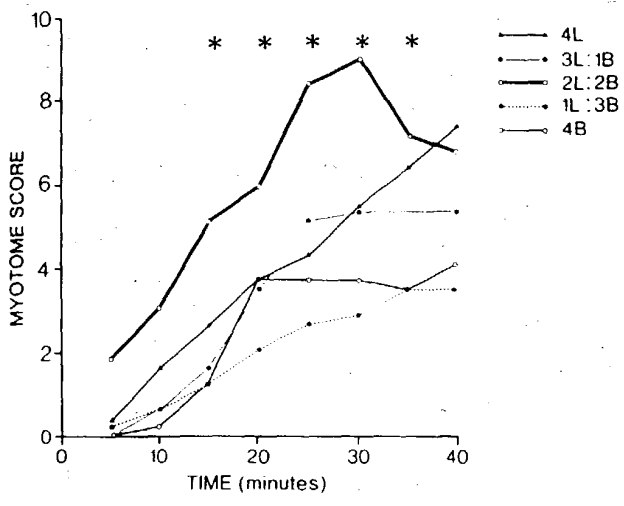

FIG. 2. Mean time-myotome score for total number of myotomes with complete motor blockade at each time interval after administration of epidural blockade (maximum possible number = 10 myotomes, *i.e.*, five for each right and left side). *Denotes significant difference among groups ($P < 0.05$).

TABLE 5. Sympathetic Blockade Indicated by the Skin Temperature at the Great Toe and Decrease in Mean Arterial Pressure (MAP) after Administration of Epidural Blockade

Group	4L	3L:1B	2L:2B	1L:3B	4B	P*
Skin temperature						
Maximum change in temperature (°C)‡	7 (0.7)	7 (0.4)	9 (0.5)	7 (1.6)	8 (0.6)	NS†
Time to initial rise (min)‡	10 (3)	8 (2)	9 (2)	7 (2)	7 (1)	NS†
Time to maximum rise (min)‡	31 (6)	25 (4)	24 (5)	21 (5)	23 (4)	NS†
Duration of maximum rise (min)‡	124 (13)	136 (20)	166 (26)	182 (27)	286 (32)	0.001
Mean Arterial Pressure						
Maximum decrease between 0–40 min (mmHg)‡	20 (4)	30 (4)	10 (2)	15 (4)	10 (4)	0.01
After induction of general anesthesia‡	15 (3)	10 (4)	15 (3)	10 (6)	10 (2)	NS†

* Probability of significant difference among the groups (Kruskal-Wallis test).

† No significant difference among the groups ($P > 0.05$).

‡ Mean (SD).

finding of similar values of T_{max} for the amide mixture components. Under these conditions toxicity would be expected to be additive, and this is supported by studies of direct intravenous infusions in monkeys.[22]

While the blood concentrations found in this study were in the range considered to be without toxicity,[16] it should be remembered that the relative toxicity of bupivacaine is approximately four times that of lidocaine.[16,22] By expressing the C_{max} values from table 6 as lidocaine equivalents (1 mg/l bupivacaine = 4 mg/l lidocaine), a comparison between the toxic potentials of the different solutions administered epidurally may be obtained. Thus, for solutions 4L and 4B, respectively, the toxic potentials are 3.2 and 2.4 mg/l lidocaine equivalents. Similarly, the toxic potentials for solutions 3L:1B, 2L:2B, and 1L:3B are, respectively, 2.1, 2.4, and 2.2 mg/l lidocaine equivalents, *i.e.*, the presence of bupivacaine does not increase the toxicity. In fact, based on intravenous data in healthy adults,[16] the presence of bupivacaine still would not increase the toxic potential even though all solutions would produce intense toxicity if rapidly injected intravenously.

In conclusion, there was little evidence of any advantage of mixing lidocaine with bupivacaine when maximum clinical doses are injected via the needle for epidural anesthesia. If an epidural catheter is inserted, individual drugs can be chosen to obtain optimal motor and sensory blockade for surgery and then sensory block without motor blockade postoperatively. Only when single-dose techniques are used does the 1:1 mixture of lidocaine-bupivacaine appear to have some merit in achieving rapid onset of motor blockade with persistence of analgesia postoperatively, although the gains are small.

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TABLE 6. Pharmacokinetic Analysis of Vascular Absorption of Lidocaine and Bupivacaine

Group	4L	3L:1B	2L:2B	1L:3B	4B	r*
C_{max}† ($mg \cdot l^{-1} \cdot 100\ mg^{-1}$)‡						
Lidocaine	0.8 (0.5)	0.5 (0.3)	0.6 (0.2)	0.7 (0.3)	—	NS§
Bupivacaine	—	0.6 (0.5)	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	NS§
T_{max} (min)‡						
Lidocaine	17 (5)	20 (8)	25 (6)	17 (9)	—	NS§
Bupivacaine	—	22 (8)	18 (9)	15 (6)	14 (6)	−0.37¶
AUC† ($mg \cdot l^{-1}\ min \cdot 100\ mg^{-1}$)‡						
Lidocaine	21 (8)	16 (7)	19 (7)	21 (9)	—	NS§
Bupivacaine	—	19 (5)	18 (5)	16 (6)	17 (6)	−0.24¶

C_{max} = maximum blood concentration achieved. T_{max} = time at which maximum blood concentration was achieved. AUC = area under concentration-time curve 0–45 min.

* Spearman nonparametric correlation coefficient for effect with increasing dose of bupivacaine.

† Note that these values are adjusted per 100 mg of agent inje

‡ Mean (SD).

§ No significant difference among the groups.

¶ $P < 0.02$.

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